EXHIBIT III.4

Expert Report of Theodore Parran
Case no. 17-OP-45004 (N.D. Ohio):
Confidential and Subject to Protective Order

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I. INTRODUCTION

1. My name is Theodore Parran, M.D. I have been retained by Plaintiffs Cuyahoga County and Summit County to offer my expert opinions on issues related to addiction medicine; issues related to treatment of pain with opioids; to evaluate the content of specific marketing messages related to addiction and pain; to address the question of whether there is an opioid epidemic in the United States, in Ohio and in Cuyahoga and Summit Counties; and, if so, what evidence-based solutions in the areas of harm reduction and treatment can be implemented to address that epidemic.

2. I have authored or coauthored numerous publications, the title and citations of which are listed on my curriculum vitae, a copy of which is **Schedule 1** to this report. This list includes publications I have authored or co-authored in the last ten years.

3. My curriculum vitae, a copy of which is Schedule 1 to this report, describes my education, background, and qualifications.

4. **Schedule 2** to my report is a list of those matters in which I have testified as an expert at trial or deposition within the past four years.

5. **Schedule 3** to my report is a list of the materials I have considered in forming the opinions contained in this report. I may be offered additional materials and may form additional opinions based on those materials.

6. **Schedule 4** is a list of the opioid products that the Defendants in this case sold or supplied. I was provided this list by counsel and unless specified will collectively refer to these drugs herein as "Defendants' Drugs."

7. **Schedule 5** is a list of common themes and messages that Plaintiffs' experts have identified were employed by Defendants in marketing and selling their opioid products. I understand that these are themes and messages that, at a minimum, will be identified in the

Expert Report of Matthew Perri, BS Pharma, Ph.D., RPh ("Perri Report"), in Section III, Table 2 and Schedule 10. I was provided this list by counsel.

8. I am being compensated at a rate of $650.00 per hour for my services in this litigation. I am also being reimbursed for all reasonable expenses incurred for my work on this litigation. No part of my compensation is contingent upon the outcome of this litigation, and I have no interest in the litigation or with either party.

9. This report contains a true and accurate statement of my opinions in this matter. The matters cited in this expert report are based on my personal knowledge, education, and years of industry experience and, if called to testify, I will testify to the same effect. These opinions are based on my education, training and experience as well as the data, evidence, and literature cited herein and listed in Schedule 3, and are offered to a reasonable degree of medical certainty. If provided with additional information, I may supplement my opinions.

II. BACKGROUND AND QUALIFICATIONS

A. Addiction treatment experience in Cleveland and throughout Northeast Ohio

10. I have been the co-medical director of Rosary Hall at St. Vincent Charity Hospital since July of 1988 and have been treating patients with addictive disease throughout Northeast Ohio since that time. In addition, I am the co-founder of the largest addiction medicine group practice in the state of Ohio, providing medical directorship services to the following agencies and organizations: the Cleveland VA Medical Center VARC, for 16 years during the 1990s and early 2000s; Stella Maris detoxification and treatment facility, for 20 of the last 28 years; the Salvation Army Harbor Light detoxification facility, for the past 20 years; the Cleveland Treatment Center methadone maintenance program, for the past 16 years; Windsor Laurelwood Behavioral Health Hospital, for the past 16 years; and Glenbeigh Hospital, for the past 12 years.

I have also been on the medical staff of University Hospitals of Cleveland, providing addiction medicine consulting expertise since 1990.

B. Addiction Training and Experience

11. My training in addiction medicine began in 1985, when I was the medical consultant to the detoxification unit at Baltimore City Hospital. I subsequently became the detox consult service director for the rest of the medical, surgical, and psychiatric units of Baltimore City Hospital, through 1988. In 1987 and 1988, I was the assistant medical director of the detoxification unit at Baltimore City Hospital. Throughout this time, I was mentored by Dr. Donald Jasinski, MD, a recently retired career researcher at the National Institute of Drug Addiction. Dr. Jasinski worked for over 20 years in the opiate research section of the National Institute of Drug Addiction.

C. Pain Management Training and Experience

12. My experience in the management of acute chronic and malignant pain began at Baltimore City Hospital during my residency training in the early 1980s. During that time, I rotated on the palliative care service as well as the Home Health Care Program, providing Home Health service to patients at the end of their lives. In 1986, as the director of the addiction consult service, it became clear that approximately one-quarter of the addiction consults that we received were actually questions regarding appropriate management of acute and chronic pain in patients with problematic behavior. I became the addiction consultant to the pain management programs at St Vincent Charity Hospital in Cleveland, starting in 1988, and at the University Hospital of Cleveland in 1990. At the University Hospital, I was the addiction consultant to Dr. Thomas Chelimski and the Department of Neurology chronic pain clinic, as well as to the acute pain anesthesia consult service in the hospital. During the early 1990s, I was the addiction consultant to the pain service at Lutheran Hospital. Since 1985, at least one-quarter of the

consultations that I have done in addiction medicine have been for advice regarding the management of acute, chronic, and malignant pain in patients suspected of having a substance use disorder. This includes inpatients as well as outpatients.

13. As a consequence of the above training and clinical experience, I have been identified as an expert witness in state and federal courts, and by several state medical boards, regarding issues involving addiction, primary care, the prescribing of controlled drugs, and pain management.

14. Owing to my experience in these issues, in 1994 four different state medical boards requested that I develop remedial education in the areas of acute and chronic pain management, anxiety and depression management, chemical dependency management, and opioid and benzodiazepine pharmacology. The result of this course development was the "Intensive Course in Controlled Drug Prescribing," one of the preeminent remedial education courses on the prescribing of controlled drugs and pain management available in the nation. This course has been held two to three times per year for the past 25 years, and over 3,500 physicians and advanced practitioners have been mandated to come for remedial education. As a consequence, I not only provide most of the education on addiction medicine, controlled drug prescribing, and the abuse potential of opioids and benzodiazepines to medical students, residents, and attending physicians in Northeast Ohio, but I also direct the only remedial course for problematic prescribers in the state of Ohio.

D. Community Involvement with Solutions to the Opioid Epidemic

15. As can be seen from my C.V., I have been active on a state-wide level since at least 1999, periodically advising the State, the Governor's office, the Medical Board and Medical Association, the Department of Health and the State Supreme Court on issues related to addition, pain management, prescription drug abuse, the opioid abuse epidemic and related medical, social

and community ramifications. Due to the volume of presentations, in-services and committees that I have been asked to participate in, those included in my C.V. are only a representative sample of my actual activities. I serve on the executive committee of the Cuyahoga County Hospital Consortium on the Opioid Crisis. I have consulted with the US Attorney's NE Opioid task force since its inception. I have consulted with the Cuyahoga County Opioid Task force since its inception. I have advised the County Director of the Alcohol and Drug Abuse Services Board (ADASB) for over 20 years. I served on the initial Board of Advisors for the first Drug Court in Cuyahoga County and have served as a drug court advisor in the County ever since. I have regularly taught seminars for the County ADASB for over two decades regarding the substance abuse issues facing our community, as well as for every one of the neighboring County boards and nearly every County ADMH Board in Northeast Ohio. I have led in-services and training on how to deal with substance abuse issues and the opioid crisis for the County and State Departments of Children and Family Services, for the State Supreme Court, and for the State Department of Corrections (out-patient probation staff).

E. Remedial Course in Controlled Drug Prescribing

16. Since 1994, I have been the course director and lead faculty member in one of the nation's pre-eminent remedial courses on the prudent prescribing of controlled drugs. As I stated earlier, this course was developed at the request of several state medical boards and has had over 3,500 mandated course participants from 48 states and 4 Canadian provinces. It focuses on pain anxiety and insomnia differential diagnosis and management, opioid and benzodiazepine pharmacology, addiction and substance use disorders and the implications for prudent and safe prescribing of controlled drugs.

F. Experience in Criminal Matters Involving Opioid Diversion

17. Over the last two decades, I have assisted law enforcement in over eighty cases – including cases being investigated by the United States Department of Justice (over 20 federal prosecutors as well as the DEA and the FBI), the Medicaid and Medicare Investigator Generals Office and, in one case, the Department of Veteran's Affairs Inspector General's Office – in evaluating criminal conduct relating to the abuse, diversion and illegal prescribing of prescription opioids

18. Through my work on these cases, as well as through my experience with addiction treatment related to Schedule II and III narcotics and my involvement in teaching courses to prescribers, I became familiar with issues related to addiction to and diversion of opioids to illicit use in Northeast Ohio, including in Cuyahoga and Summit Counties.

III. OPINIONS

19. For the reasons discussed in detail below, *see* Section IV, I offer the following opinions:

20. Opioids are, and always have been, dangerous drugs having a high risk of dependence and addiction and associated high rates of morbidity and mortality.

21. While opioids can be successfully prescribed to treat acute pain and have been used to treat cancer and end-of-life pain, their side effects of euphoria, craving, sedation, respiratory depression, tolerance and dependence make them risky to administer for long durations, particularly at high doses.

22. Tolerance is an effect in which the body acclimates to a substance so that, over time, larger doses are required to produce the same effect. Tolerance to opioids can occur very quickly after initiation of the drug and regular use. Tolerance is a common side effect of opioids, which means that to produce the same pain relief over a long period of time, larger doses are

required. But tolerance is not uniform across all effects, so that the escalating doses required to provide pain relief may produce dangerous levels of other side effects, such as sedation and respiratory depression.

23. It is simply not true that dosage of prescription opioids can always be safely increased with no ceiling. In addition, the high dosage pills necessary for effective pain relief in individuals who have developed a high degree of tolerance are especially dangerous – and indeed, can be lethal – if ingested by individuals who have not developed the same degree of tolerance.

24. Without a large population that has developed tolerance to modest doses of opioids, there would be no reason for a large population to be exposed to high doses of opioids (greater than 50 MMEs per day).[1] Indeed, it is very dangerous to expose a large population in general, and an opioid naïve population in particular, to high-dose opioids.

25. Physical dependence is an almost universal consequence of opioid use. There are many serious physical consequences of opioid dependence and they should never have been downplayed.

26. Patients can become physically dependent to opioids in as little as a few days to several weeks.

27. One factor that affects the extent and timing of dependence is dose, with higher doses resulting in faster and more intractable dependence.

[1] When I refer to "high doses" herein, I will define that term as doses exceeding 50 MME/day. *See* Deborah Dowell et al., *CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016*, 65 Morbidity and Mortality Weekly Report 1 (Mar. 18, 2016), at 23, https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm (noting "Most experts agreed that, in general, increasing dosages to 50 or more MME/day increases overdose risk without necessarily adding benefits for pain control or function.") (hereinafter "CDC Guideline").

28. Once physically dependent, patients will experience withdrawal if opioids are reduced or discontinued. Withdrawal can be excruciatingly painful and can present difficult clinical challenges. The severity of the withdrawal always increases with dose and duration of opioids taken.

29. Tapering off high doses of opioids can be very challenging clinically, often resulting in the triggering of withdrawal and increasing the risk of misuse, diversion or return to opioids. Once a patient is exposed to opioids at high doses and for long durations, it is often *very* difficult to remove that patient from opioids.

30. A significant portion of patients exposed to opioids will develop Opioid Use Disorder. Opioid Use Disorder ("OUD" or "addiction" to opioids) is a chronic disease with a high rate of relapse. (I also refer to OUD as addiction or "addictive disease" herein). OUD is defined by a cluster of diagnostic criteria that include loss of control, craving, devotion of significant time to obtaining and using opioids, reduction of other social and recreational activities, tolerance, and withdrawal. Depending on how many of the diagnostic criteria are present, a patient may be diagnosed as having "mild," "moderate," or "severe" OUD. The term "addiction" is generally used to refer to patients with moderate or severe OUD, but even patients whose OUD is "mild" and who may not be considered "addicted" may require addiction treatment and many will require a course of treatment to remove them from the drugs.

31. Development of the disease of opioid addiction in individuals generally occurs as the result of three primary groups of factors: biology (genetics), environment, and exposure. The key factor is exposure; biology and environment do not factor into the equation unless patients are exposed to the chemicals. In other words, if people are not exposed to opioids, the other factors do not trigger addiction.

32. The opioid epidemic we have today was a direct result of the massive exposure of a wide swath of the United States to prescription opioids. The Defendants, the companies that manufactured, sold and distributed prescription opioids, caused that exposure.

33. While not all people who are exposed to opioids will develop addictive disease, a significant number will. The risk of addiction certainly is not rare when patients are exposed to opioids for long-term use. Studies have shown that between 8% and 12% of patients prescribed chronic opioids develop a moderate to severe opioid use disorder (approximately 1 in 10), while approximately two to three times that percentage (20-30%) develop milder forms of OUD, according to the number of diagnostic criteria met for each level of severity.

34. It is impossible to completely and accurately predict which people will become addicted with exposure and, therefore, it was highly risky and inappropriate for Defendants to market the use of these drugs for a wide swath of the population and a wide array of pain conditions.

35. It is especially difficult for doctors outside the addiction medicine specialty, who typically have little training regarding addiction, to try to identify the patients who might develop addictive disease prior to prescribing opioids. Therefore, Defendants' marketing of opioids to a wide variety of physician specialties to treat a wide range of conditions, with the message that predicting, and then screening out, those who would become addicted is easily done was false, misleading and put patients at risk.

36. There is no evidence, and never was, that patients with legitimate pain cannot develop OUD or do not become physically dependent. There is no basis to believe that pain "protects" patients taking opioids from any of the side effects of euphoria, craving, sedation, respiratory depression, tolerance, addiction, misuse and dependence associated with opioids.

37. The myth that patients taking opioids for pain cannot become addicted or suffer harmful consequences is particularly harmful and wholesale untrue. It has long been known that opioids are addictive and that these drugs are controlled substances categorized as Schedule II (or for some opioids, Schedule III) narcotics. The myth that patients taking opioids for pain do not become addicted, however, lulled doctors into believing that what they otherwise knew about opioids did not apply to patients with legitimate diagnoses of pain and was only relevant to an invisible population of "addicts" who were not their patients.

38. It is not the case that only those seeking the euphoric feeling that opioids can produce will misuse them. Avoiding painful withdrawal is as compelling a motivator, if not a more compelling one, for non-medical use, and affects even patients taking opioids as prescribed by a doctor.

39. It was foreseeable that increased exposure to opioids associated with increased prescribing of opioids would increase misuse, addiction, dependence, and diversion of opioids.

40. When people are prescribed opioids, particularly for long durations, a significant percentage will misuse or become addicted to opioids; there is no clinical basis to assume that the risk of addiction or dependence for long-term opioid prescribing is rare. If you increase the number of patients who are prescribed opioids, you will, of necessity, increase the number who misuse and/or become addicted. If the number of people prescribed opioids in a community is high, the number of people who misuse and/or become addicted to opioids will be correspondingly high.

41. The dangers described in Paragraphs 19-40 and more fully within this report, were well known and are reflected in many scientific studies published over decades.

42. Conversely, there was, and is, no credible science to support the conclusion that long-term opioid prescribing is an effective treatment for pain in any significant number of patients.

43. While there likely is a small percentage of patients who feel they benefit, or do benefit, from opioid treatment for pain, it is difficult to identify those patients prior to initiation of long-term treatment with opioids.

44. There is no real objective standard or bright line test delineating when opioids are appropriately given for long-term use or to treat chronic conditions. At most, opioids are properly indicated for the short-term treatment of moderate to severe acute pain (e.g. trauma or post-surgical pain); end-of-life pain/hospice care; and cancer pain from active malignant disease. Chronic opioid therapy is not recommended for most common chronic pain conditions (defined as moderate to severe pain lasting beyond 90 days), including low back pain, centralized pain such as fibromyalgia, and headache pain. In less common moderate to severe chronic pain conditions (such as pain from advanced multiple sclerosis, sickle cell disease, pain following spinal cord injury and paraplegia, or post-herpetic neuralgia), which comprise a small percentage of chronic pain patients, opioids may be considered a third-line therapy (taken if other therapies are ineffective or contraindicated).

45. Given the narrow criteria for indicated chronic pain use, its role as third-line therapy, and the significant risks associated with its use, chronic opioid therapy for persons with chronic pain conditions is, at most, indicated in less than 10% of patients with chronic pain and likely significantly fewer. Among all opioids prescribed for long-term use (i.e. prescriptions written for 90 days, or 30 days with refills, including for acute conditions), this percentage is much smaller. For all proper indications other than hospice care, if prescribed, opioids should

be prescribed with the lowest effective dose of preferably immediate-release opioids, taken only when needed and only as long as necessary.

46. There have been no consistent, objective standards for doctors to apply to prospectively identify the small minority of patients who might benefit from long-term opioid treatment for chronic pain and to distinguish those people from the vast majority for whom opioids will not work long-term. The only way to determine who the small population is who may benefit from long-term opioid treatment is retrospective, after the course of treatment has been performed. Evaluating such a benefit retrospectively would not be inappropriate if there was not also such a substantial risk of exposing patients to serious risks by doing so. However, such an experiment is generally inappropriate because of the serious risks of opioids.

47. Opioids should not be, and should never have been, used as a first-line chronic pain treatment in lieu of other conventional, non-opioid treatment options and, in most patients (other than in acute settings or for palliative care), opioids should not be considered as a choice at all.

48. Exposing the brain to opioids at a high dose over an extended period of time also seems to alter the underlying brain and other components of the nervous system structure, leaving it more sensitive to withdrawal and, in some cases, more sensitive to pain. This effect has been termed hyperalgesia. Patients who experience pain while on opioids, or upon discontinuation, may believe that opioids are necessary to control their underlying pain, and are often unaware that opioids may actually be contributing to their pain.

49. For acute pain conditions, including post-surgery, opioid therapy should be used for only a very short period of time, not to exceed one or two weeks; in many instances of acute pain, two to five days of opioids is sufficient.

50. Beginning in the late 1980's, and accelerating from the mid-1990's, there was a dramatic change in clinical use of opioids in the United States, as doctors were increasingly told to focus on relieving pain in all patients. It was my view then, and continues to be my view now, that those promoting this change in clinical practice tended to trivialize addiction and unreasonably expose patients to the risk associated with opioids.

51. There is no reason to believe that the prevalence of pain in the United States should be dramatically higher than other developed countries, and there is no medical rationale for the fact that the United States is the largest consumer of opioids in the world, including consuming over 99% of the world's hydrocodone and over 72% of the world's oxycodone in 2016.

52. I have reviewed the summary of common marketing themes and messages that I under Plaintiffs' experts have identified were delivered by Defendants in marketing and sales of their opioid products summarized in Schedule 5 to my report). It is my opinion that the marketing themes and messages summarized in Schedule 5 are either false, inaccurate, incomplete and/or designed to mislead or give prescribers and patients a false sense of security and/or mislead prescribers and the public about the risks and benefits of opioids as set forth more fully below (*see infra* Section IV.H) including the following themes and messages:

a. <u>Themes:</u>

i. Dependence, tolerance, addiction and withdrawal should not be a concern in prescribing opioids.

ii. Opioids are effective for, and improve functioning in, patients taking them for long-term and chronic use.

iii. Opioids should be a first-line therapy for pain.

b. Messages:

i. Extended release drugs, and/or q12 dosing, had fewer peaks and valleys and less chance of addiction and abuse.

ii. Abuse deterrent formulations deter abuse.

iii. Abuse deterrent formulations are safer than non-abuse deterrent formulations.

iv. Minimize concerns about addictive nature of opioids.

v. Science now showing opioids are not as addictive as once thought.

vi. True patients in pain cannot get addicted – pain protects against addiction.

vii. Signs of addiction as simply symptoms of undertreated pain or "pseudoaddiction."

viii. Problems only occur when opioids are abused or used illegally-addicts are bad people who knowingly abused the drugs, not good people who were seeking treatment for legitimate ailments.

ix. If taken as prescribed, risk is almost nonexistent.

x. Addiction less than 1% or low or rare.

xi. Patients can be easily tapered off opioids.

xii. Dependence is not a significant concern - only physical and easily reversed.

xiii. Drug abusers and potential addicts can be easily identified and therefore not prescribed opioids, or prescribed opioids and monitored closely.

xiv. Even patients at high risk of addiction can be safely prescribed opioids by using risk-mitigation strategies such as pain contracts.

xv. Pain should be treated with opioids.

xvi. Undertreated pain should be treated with opioids.

xvii. There is more risk of leaving pain untreated than using opioids to treat pain.

xviii. Opioids offer more effective pain control and are safer than alternatives.

xix. Defendants' opioids will make your life better.

xx. No maximum dose- if you are in pain more opioids could be given without additional risk (i.e., "titrate to effect" concept from cancer/palliative care should be used with chronic pain).

xxi. Opioids can be prescribed for any pain condition without risk.

xxii. Opioids can be prescribed to any age group without risk.

xxiii. "Round the clock" dosing should be used for chronic pain rather than "as needed" dosing.

xxiv. "Breakthrough pain" applies to chronic pain, not just cancer pain, and short-acting opioids should be used to supplement long-acting opioids for that reason.

53. I was provided with and have reviewed a number of publications that Plaintiffs allege were funded by Defendants and used by Defendants to improperly expand the market for prescription opioids and to distribute false or misleading messages about prescription opioids (listed at i. to x. of this Paragraph). I have the opinions that these documents either contain statements that were inaccurate or misleading and/or that Defendants' reliance on these

documents to greatly expand the market for opioid treatment was improper or misleading. *See infra* Section IV.I. This list includes:

i. Porter, Jane, and Hershel Jick. "Addiction rare in patients treated with narcotics." The New England journal of medicine 302.2 (1980): 123.

ii. Portenoy, Russell K., and Kathleen M. Foley. "Chronic use of opioid analgesics in non-malignant pain: report of 38 cases." Pain 25.2 (1986): 171-186.

iii. "The Use of Opioids for the Treatment of Chronic Pain: A consensus statement from the American Academy of Pain Medicine and the American Pain Society." (1997)

iv. Federation of Medical Boards of the United States, Inc. "Model Guidelines for the Use of Controlled Substances for the Treatment of Pain". May 2, 1999.

v. Berry, Patricia H., et al. "Pain: current understanding of assessment, management, and treatments." National Pharmaceutical Council and the Joint Commission for the Accreditation of Healthcare Organizations, VA, USA (2001): b44.

vi. Joint Commission on Accreditation of Healthcare Organizations. "Joint Commission on Accreditation of Healthcare Organizations pain standards for 2001." (2001).

vii. AGS Panel on Persistent Pain in Older Persons. "The management of persistent pain in older persons." Journal of the American Geriatrics Society 50.6 Suppl (2002): S205.

viii. Federation of Medical Boards of the United States, Inc. "Model Policy for the Use of Controlled Substances for the Treatment of Pain". 2004.

ix. Fishman, Scott. "Responsible opioid prescribing: a clinician's guide". Waterford Life Sciences, 2007.

x. Chou, Roger, et al. "Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain." The Journal of Pain10.2 (2009): 113-130.

54. The current state of the addiction treatment ecosystem is significantly lacking to handle the amount of addicted, misusing and dependent patients in Cuyahoga and Summit Counties and the surrounding communities.

55. While resources are currently lacking, there is a standard and evidence-based course of treatment for members of the community who have OUD and/or are misusing opioids (discussed more thoroughly *infra* Section IV.K) that can and should be implemented in Summit and Cuyahoga Counties and that includes:

i. Medication Assisted Treatment ("MAT")

ii. Psychological Therapy

iii. Social Support

56. Access to treatment and immediate referral to treatment are key components of a successful treatment ecosystem that must be improved, with resources, in Cuyahoga and Summit Counties to help address the opioid epidemic in those communities.

57. In crafting a solution to the opioid epidemic in Cuyahoga and Summit counties, it is important to create a treatment solution not only for the population who is misusing and addicted to opioids, but also for the population who are physically dependent on opioids. That treatment solution should include the multi-modal chronic pain management interventions, specialty consultation, physical and psychological interventions, and initiation of opioid tapers or

other interventions (OTP with buprenorphine or methadone or acute medical opioid withdrawal management).

IV. DETAILED STATEMENT OF OPINIONS AND BASIS FOR OPINIONS

A. Definitions

58. For purposes of this report, I have utilized terms with the following definitions:

i. Addiction or Addictive Disease: Addictive disease is a clinical term that describes alcoholism and drug addiction.[2] The American Society of Addiction Medicine ("ASAM") defines addiction as "a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death." [3]

[2] Lauren M. Broyles et al., *Confronting Inadvertent Stigma and Pejorative Language in Addiction Scholarship: A Recognition and Response*, 35(3) Subst. Abus. 217 (2014), https://www.ncbi.nlm.nih.gov/pubmed/24911031.

[3] *See* Short Definition of Addiction, ASAM (Apr. 12, 2011), https://www.asam.org/resources/definition-of-addiction. This is the short definition of addiction. For the ASAM long definition of addiction, *see also*, Kyle Kampman & Margaret Jarvis, *American Society of Addiction Medicine (ASAM) National Practice Guideline For the Use of Medications in the Treatment of Addiction Involving Opioid Use*, 9 J. Addict. Med. 1, 3 (2015).

ii. Chronic Pain: Pain that typically lasts for more than 3 months, or past the time of normal tissue healing.[4]

iii. Defendants' Drugs: The opioid products Defendants in this matter sold or distributed, a list of which has been attached hereto as Schedule 4 to my report.

iv. Dependence: A state of adaptation that is manifested by a drug-class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.[5]

v. Medical Use of Prescription Opioids: the use of opioids as prescribed by a physician and taken as directed by a physician.

vi. Misuse: Use of prescription drugs in any way that a doctor did not direct a person to use them, including (1) use without a prescription of the patient's own; (2) use in greater amounts, more often, or longer than the patient was told to take them; or (3) use in any other way a doctor did not direct the patient to use them.[6]

vii. Non-Medical Use of Prescription Opioids: *see* definition of "misuse" above.

viii. Opioid use Disorder (OUD): (See definition of Addiction above.) The American Psychiatric Association (APA) has developed a "diagnostic and statistical manual" ("DSM") to clinically define psychiatric diseases. This DSM has gone through several

[4] CDC Guideline, *supra* note 1.

[5] Kampman & Jarvis, *supra* note 3, at 11.

[6] SAMSHA *National Survey on Drug Use and Health: Comparison of 2015-2016 and 2016-2017 Population Percentages (50 States and the District of Columbia)* at 3, https://www.samhsa.gov/data/data-we-collect/nsduh-national-survey-drug-use-and-health.

iterations or editions over the past five decades, with the most recent being the DSM-V. The DSM defines what has historically been called addictive disease or chemical dependence under the umbrella term of "substance use disorder" or, in the specific instance of opioid addiction, "Opiate Use Disorder." The DSM-V lists a series of 11 Diagnostic Criteria. Patients are classified as having mild OUD if they meet 2-3 of those criteria, moderate OUD if they meet 4-5 of the criteria and with severe OUD if they meet 6 or more. Opioid Use Disorder moderate or severe typically involves loss of control over opioid use, compulsive use of opioids, continuation of use in the face of adverse consequences, and craving for the opioids once they are no longer available. Moderate or severe Opioid Use Disorder is generally in line with Addiction to opioids as defined by the ASAM above and is a devastating clinical disease state with high rates of mortality and morbidity, with the leading causes of death in people using opioids for non-medical purposes being overdose and trauma. Patients with mild Opioid Use Disorder are not free of risk or serious consequences and often require treatment.

ix. Tolerance: A decrease in response to a drug dose that occurs with continued use. If an individual is tolerant to a drug, increased doses are required to achieve the effects originally produced by lower doses.[7]

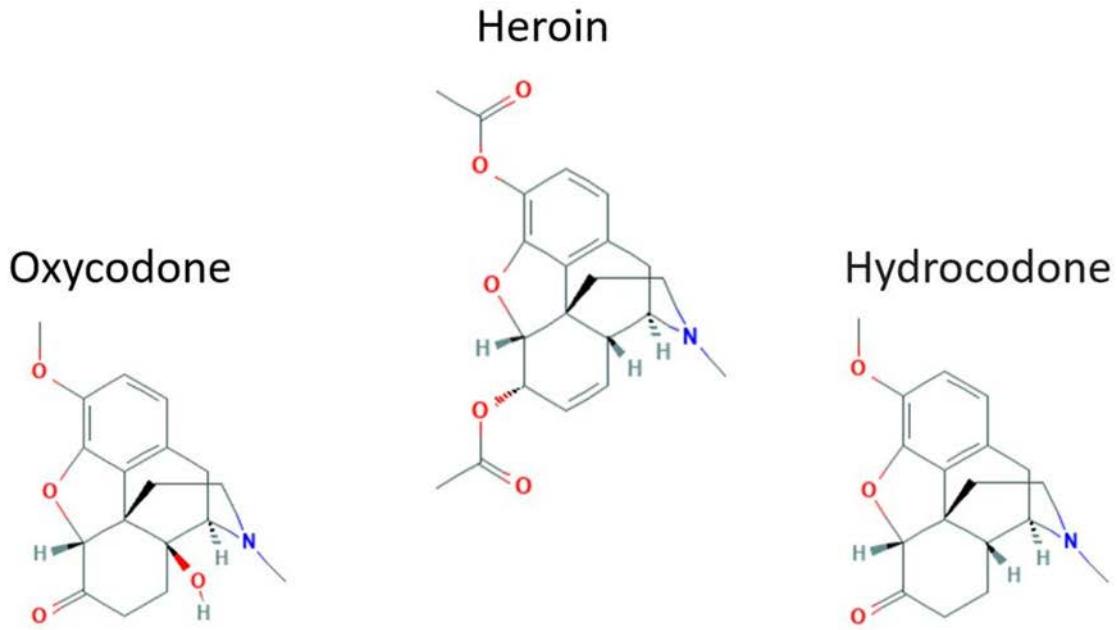
59. Even though these are defined terms in the specialty of addiction medicine, the difference between several of these terms –OUD, dependence, misuse and addiction– is not always a distinct line because these various states sometimes overlap and are not always capable of clear, objective delineation. However, wherever possible, the terms used will have the meaning set forth above.

[7] Kyle Kampman et al., *National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use*. ASAM (June 1, 2015), at 11.

B. Opioids and Their Known Risks.

1. The Biochemistry and the Effects on the Brain and the Body

60. Opioids are a class of drugs found in the opium poppy plant. While there are different types of opioids, the chemical structure of many is nearly identical:[8]



61. There are different types of opioid agonists and opioid antagonists. (E.g., naloxone to reverse overdoses and naltrexone, which is longer acting and used in treatment, *see infra* Section IV.K.1.d; opioid partial agonists, e.g., buprenorphine- used in treatment- *see infra* Section IV.K.1.c; lower potency agonists; and higher potency agonists, e.g., heroin, oxycodone, fentanyl, morphine and hydromorphone.)[9]

[8] Nat'l Inst. on Drug Abuse, *Drug Facts: What are Prescription Opioids*?, (June 2018), https://www.drugabuse.gov/publications/drugfacts/prescription-opioids.

[9] *American Society of Addiction Medicine (ASAM), Handbook on Pain and Addiction* (Ilene Robeck, M.D., et al. eds. 2018) 89-90.

62. The high potency agonists are the drugs most capable of producing analgesia. They are also the group of opioids with the greatest addiction risk and the highest risk of overdose and death.[10]

63. Additionally, there are short-acting opioids (SAOs) and long-acting opioids (LAOs). Short-acting opioids rapidly flood the brain with high levels of the drug and can be useful for acute pain relief when the goal is to relieve pain very quickly.[11] Long-acting opioids typically have been used to treat chronic pain rather than acute pain. As instructed by ASAM, "clinicians should not assume that LAOs are therefore safer or less addictive than SAOs. LAOs can be quite addictive and their use is associated with high levels of tolerance and withdrawal."[12]

64. Opioids as a class of drugs interact with the mu or kappa receptors in the brain, spinal cord, and other areas of the body, especially those involved in feelings of pleasure and pain. The opioid system, and how prescription opioids interact with this system, is complex. Opioids produce an analgesic effect by reduction in transmission of pain messages in the spinal cord.

65. In addition to the analgesic effects of opioids, the drug also targets the brain's reward system by flooding the circuit with dopamine. Dopamine is a neurotransmitter present in regions of the brain that regulate movement, emotion, motivation, and feelings of pleasure. When activated at normal levels, this system rewards our natural behaviors. Overstimulating the system with drugs, however, produces euphoric effects, which strongly reinforce the behavior of

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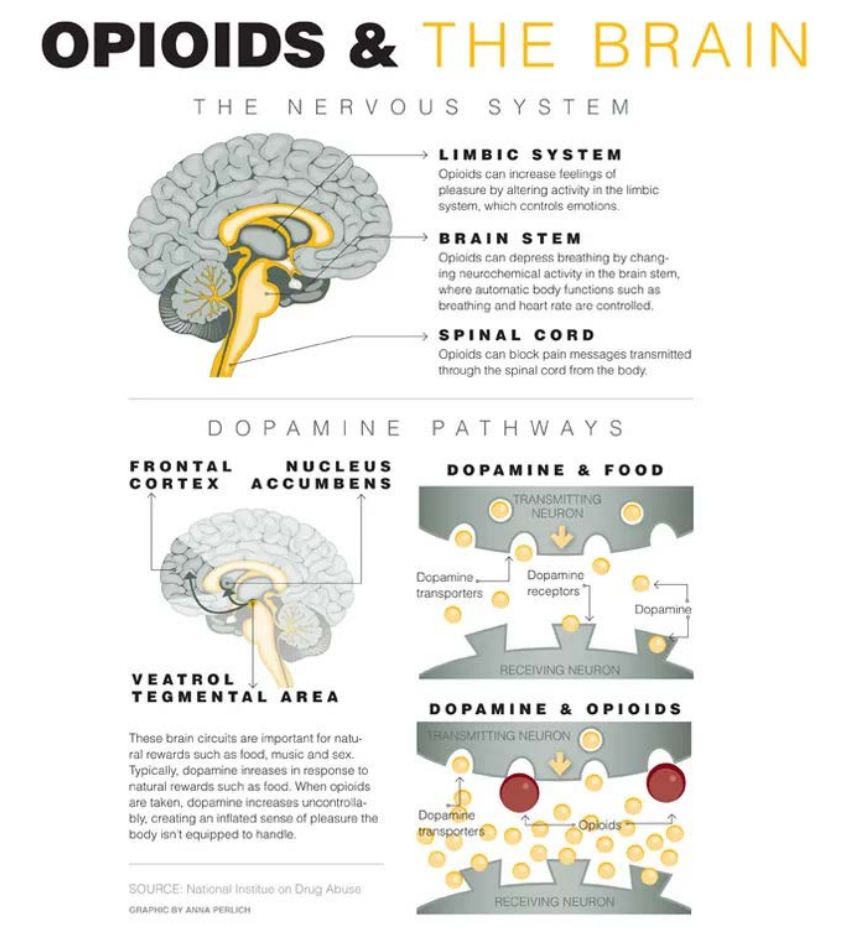
[10] *Id.*

[11] *Id.* at 88.

[12] *Id.* at 89.

drug use—teaching the user to repeat it. This euphoria effect of opioids is a non-therapeutic side effect.

66. The following graphic from the National Institute on Drug Abuse is a basic illustration of opioids' effect on the brain and the body:[13]



2. Mortality Risk

67. In addition to analgesic effects, opioids also have well-known and serious dangers associated with them, including a risk of respiratory depression, addiction, dependence, overdose and death.

[13] Graphic by Anna Perlich, National Institute on Drug Abuse, https://www.drugabuse.gov/.

68. As the graphic above illustrates, opioids affect the central part of the brain that regulates breathing. The drug slows down breathing and can cause fatal respiratory depression.

69. As opioid doses increase, so does the risk of profound opioid-induced respiratory depression that causes the person to stop breathing, which in turn causes the oxygen supply to the brain and heart to plunge and the victim dies from cardiac arrest secondary to respiratory arrest.

70. Over the last decade, the United States has seen opioid overdose deaths rise in startling numbers:

a. From 1999-2017, more than 700,000 people died from an opioid overdose;[14]

b. Every 11 minutes, a person dies of an opioid overdose;[15]

c. Opioid overdose death is the #1 cause of death in people under the Age of 50;[16]

d. Opioid overdoses account for 1 out of every 5 deaths of persons Ages 25-34;[17]

[14] *Opioid Overdose, Understanding the Epidemic*, Centers for Disease Control and Prevention (Dec. 19, 2018), https://www.cdc.gov/drugoverdose/epidemic/index.html.

[15] *Drug Overdose Deaths in the United States, 1999–2017*, Centers for Disease Control and Prevention (Nov. 2018), https://www.cdc.gov/nchs/products/databriefs/db329.htm.

[16] *U.S. Life Expectancy Declining: Do Opioid Overdose Deaths Play a Role?*, CO*RE, (Jan. 31, 2018), http://core-rems.org/u-s-life-expectancy-declining-do-opioid-overdose-deaths-play-a-role/.

[17] Tara Gomes, et al., *The Burden of Opioid-Related Mortality in the United States*, JAMA (June 1, 2018), https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2682878.

e. In 2017, over 130 people ***per day*** died in the United States as a result of an opioid overdose; [18]

f. Drug overdose, driven primarily by opioids, is now the leading cause of unintentional injury death in the United States,[19] and

g. In 2007, unintentional drug poisoning became the leading cause of injury death in Ohio, surpassing motor vehicle crashes for the first time on record. This trend has continued through 2017.[20] From 2000 to 2017, Ohio's death rate due to unintentional drug poisonings increased 1,081 percent, and the increase in deaths has been driven largely by opioid-related overdoses.[21]

3. Dependence, Misuse and Addiction

71. Mortality is just one of several severe consequences related to opioid use. Other risks associated with opioids, including dependence, misuse and addiction, have been well known throughout history and have presented themselves in significant numbers in the current opioid epidemic.

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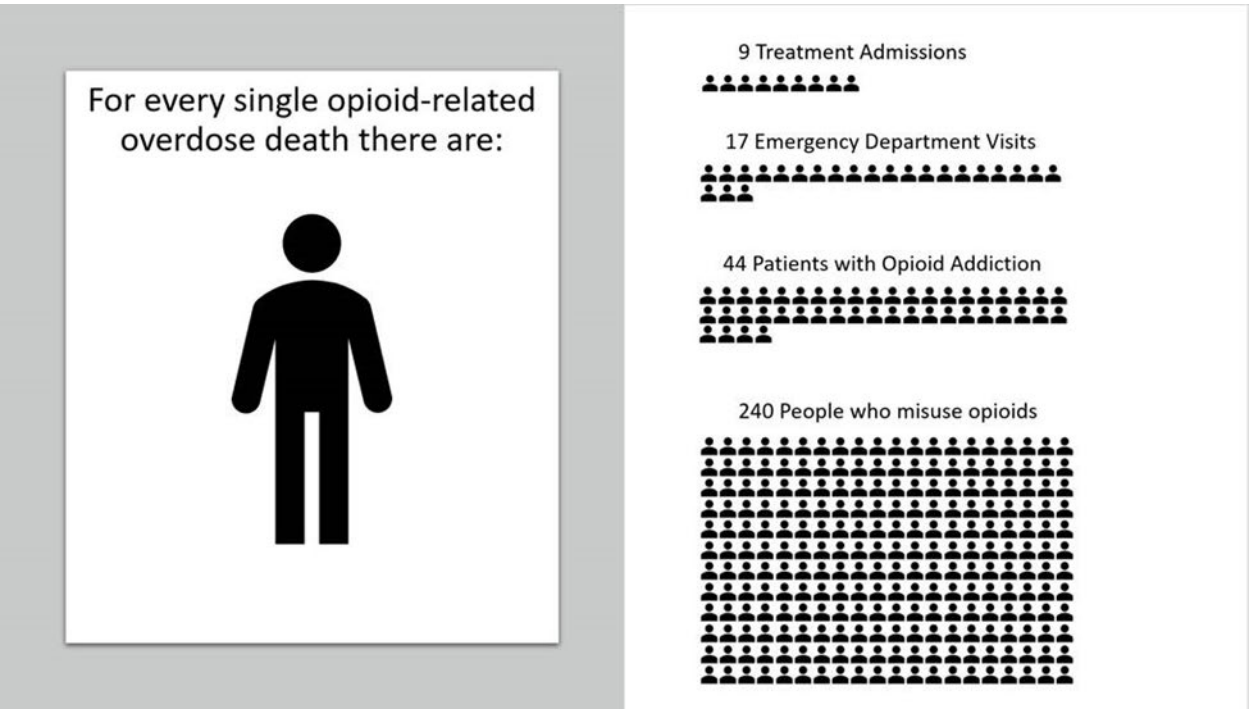
[18] CDC/NCHS, National Vital Statistics System, *Mortality*. CDC WONDER, https://wonder.cdc.gov.

[19] Nat'l Acads. of Science, Eng'g and Medicine, *Pain Mgmt. and the Opioid Epidemic* (2017) at 17 (citing Rose Rudd, et al., 65 *Morbidity and Mortality Weekly Report*, 50-51, 1445-52 (2016)).

[20] *Drug Overdose*, Ohio Dep't of Health (July 2, 2018), https://odh.ohio.gov/wps/portal/gov/odh/know-our-programs/violence-injury-prevention-program/Drug-overdose/drug-overdose.

[21] *Id.*

72. Indeed, as the following graphic illustrates, for every opioid overdose and death, there are many more instances of people who have opioid addiction, who abuse or misuse opioids, who are dependent on opioids or who take them for non-medical purposes:[22]



73. In 2017, 47,600 people in the United States died of an opioid overdose.[23] 2017 data reported that 2,110,000 people suffered from OUD, and 11,401,000 used opioids for non-medical uses (misuse).[24] These numbers are derived from survey data and are largely

[22] Graphic uses 2017 data from the following sources: *Overdose Death Rates*, NIH (Jan. 2019), https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates; *SAMHSA/HHS: An Update on the Opioid Crisis*, SAMHSA (Mar. 14, 2018), https://www.samhsa.gov/sites/default/files/aatod_2018_final.pdf at Tables 7.2, 7.28, and 7.34; *HCUP Fast Stats*, Healthcare Cost and Utilization Project (HCUP) (Oct. 2018), www.hcup-us.ahrq.gov/faststats/opioid/opioidusemap.jsp?setting=IP.

[23] *Overdose Death Rates*, NIH (Jan. 2019), https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates (original data source: CDC WONDER, https://wonder.cdc.gov/)

[24] *Results from the 2017 National Survey on Drug Use and Health: Detailed Tables*, Center for Behavioral Health Statistics and Quality (CBHSQ) et al., at Tables 7.2, 7.28, and 7.34,

undercounted. They do not take into account large populations like the homeless and prison populations. Further, they do not take into account the millions of people who are dependent on prescription opioids and are unable to stop taking the drugs (a significant population who must be addressed in efforts to combat the epidemic). But nonetheless, they show in part the severe and profound effect of exposing a wide swath of people to prescription opioids.

74. Understanding how so many people have become addicted to or dependent on opioids and have begun to misuse them requires understanding how opioids affect the brain and the body, especially when used long term.

a. Tolerance

75. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

76. As described above, opioids stimulate mu receptors resulting in a decreased sensation of pain, much like the brain's own endorphins work. In addition, opioids produce a dopamine surge in the brain that is euphoria-producing.

77. Typically, the brain balances its own endorphins. When an external source (here an opioid) floods the brain's mu receptors that endogenous endorphin system is distorted. That opioid effect tells the brain that pain is relieved, and the dopamine surge tells the brain that the drug is pleasurable.

78. The brain responds to opioids – and the opioid-induced changes in pain via mu receptors and associated surges in dopamine opioids – by beginning to change circuits in the brain over time, initially creating tolerance and then physical dependence. In those with

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https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2017/NSDUHDetailedTabs2017.htm#lotsect1se.

addictive disease, the opioids also produce the desire for more and more opioids. The strong release of dopamine reinforces the act of taking the drug, making the user want to repeat the euphoric experience. By the same token, however, withdrawal also serves as a reinforcing mechanism as the anxiety and physical effects of withdrawal, described below, increases the cost of ceasing to use opioids. As such, whether a person falls under the definition of addiction, OUD or has dependence, the consequences can be significant, including being life-altering or fatal.

79. As tolerance increases over time, higher doses are needed to achieve the same therapeutic impact and the same euphoric feeling.[25] Additionally, tolerance leads to a decrease in opioid effect with repeated administration.[26] Thus, prescribing opioids long-term for their analgesic effects will typically require increasingly higher doses in order to maintain the initial level of analgesia — up to 10 times the original dose over an extended period of time.[27]

80. As Curtis Wright, M.D., the FDA's Medical Review Officer for OxyContin who later became Executive Director, Medical Affairs and subsequently Executive Director of Risk Assessment for Purdue, explained, "[t]olerance is a defensive reaction by the body to the administration of opioids, and it develops in everybody who takes an opioid … The longer the drug is in and the higher the level of the drug, the more tolerance you get."[28]

81. We have seen a substantial number of patients who, because of the tolerance producing aspects of the drug, end up on daily doses of up to 800 morphine milligram

[25] Nora Volkow, et al., *Opioid Abuse in Chronic Pain-Misconceptions and Mitigation Strategies*, 374 N. Engl. J. Med. 1253, 1256 (2016).

[26] *Id.*

[27] *Id.*

[28] Curtis Wright Dep. Tr. 159:12-160:20, Dec. 19, 2018.

equivalents per day (MME, the conversion factor used to facilitate comparison of potency among opioids). These kinds of doses would almost certainly cause overdose and death in an opioid naïve person and present a significant risk of overdose even in a person with tolerance.

82. As Volkow observes, the tolerance aspect to opioid drugs is particularly dangerous because tolerance to the analgesic and euphoric effects of opioids develops quickly, whereas tolerance to respiratory depression develops more slowly.[29] This creates a situation where increases in dose by the prescriber or patient to maintain analgesia (or euphoric reward) can markedly increase the risk of severe respiratory depression or overdose.[30]

83. Indeed, for anyone to suggest that dependence on or tolerance to opioids is not a serious condition, or that the people who do not meet the current definition of addiction are not at serious risk if dependent on opioids, is utterly false. Further, for any Defendant to have said that those who are simply "dependent" and not at risk is highly inappropriate and highly dangerous.

b. Dependence and Withdrawal

84. While seeking the euphoric feeling that opioids can produce is a strong motivator for continued opioid use, an even more compelling motivator for continued use is often avoiding

[29] Nora Volkow, et al., *Opioid Abuse in Chronic Pain-Misconceptions and Mitigation Strategies*, 374 N. Engl. J. Med. 1253, 1256 (2016) (citing Rob Hill, et al., *Ethanol Reversal of Tolerance to the Respiratory Depressant Effects of Morphine*, 41 Neuropsychopharmacology 762-73 (2016), https://www.ncbi.nlm.nih.gov/pubmed/26171718; GS Ling, et al., *Differential Development of Acute Tolerance to Analgesia, Respiratory Depression, Gastrointestinal Transit and Hormone Release in a Morphine Infusion Model*, Life Sci. (1989) 45: 1627-36, https://www.ncbi.nlm.nih.gov/pubmed/2555641).

[30] *Id.*

the powerful and negative side effects that occur when a person abruptly stops taking the drug while physically dependent.[31]

85. One unique issue with opioids is how quickly those who take them can become physically dependent, especially when taken on a daily basis (as with LAOs) rather than as needed for pain. Indeed, with daily exposure to opioids, very early evidence of physical dependence can be detected after several days to a few weeks.[32]

86. This may explain why the transition from an initial opioid prescription to chronic use begins very early on.[33] As reported in the CDC data, even a one-day opioid prescription carried a 6 percent risk of use at one year later and a 2.9 percent risk of use at three years later.[34] The sharpest increases in the likelihood of long-term use came at five days after the initial prescription, with another spike was seen at one month.[35] Patients given a prescription for a longer duration at the outset —a week or a month—were the most likely to fall into long-term

[31] Thomas R. Kosten, et al., *The Neurobiology of Opioid Dependence: Implications for Treatment*, 1 Science Practical Perspective. 1, 13–20 (2002), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2851054/ ("Brain abnormalities resulting from chronic use of heroin, oxycodone, and other morphine-derived drugs are underlying causes of opioid dependence (the need to keep taking drugs to avoid withdrawal syndrome) and addiction (intense drug craving and compulsive use)").

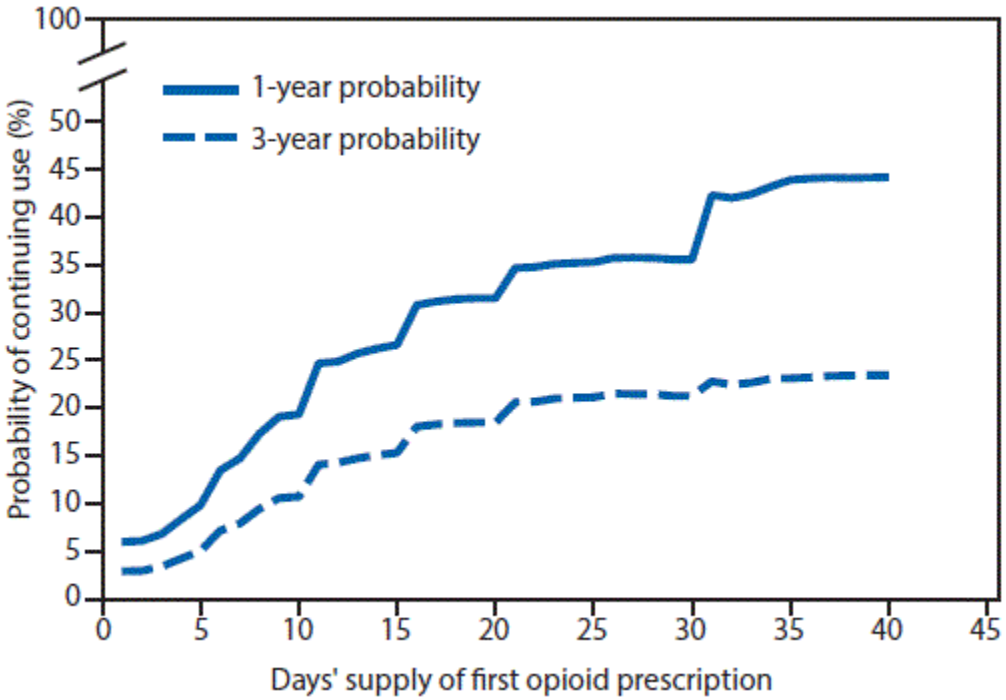
[32] Chris P. Bailey & Mark Connor, *Opioids: Cellular Mechanisms of Tolerance and Physical Dependence*, 5 Current Opinion in Pharmacology 1, at 60, https://www.ncbi.nlm.nih.gov/pubmed/15661627.

[33] Anuj Shah, et al., *Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use- Unites States, 2006-2015*, Morbidity and Mortality Weekly Report (Mar. 17, 2017), https://www.cdc.gov/mmwr/volumes/66/wr/mm6610a1.htm.

[34] *Id.*

[35] *Id.*

use.[36] Among people given enough pills for eight days or more, 13.5 percent were still using them a year later. Among those given a month-long prescription, that rate climbed to 30 percent.[37]



87. Once physical dependence develops, abrupt discontinuation of the opioid drug will trigger brain and body responses that are opposite of the opioids' effects. This is termed opioid withdrawal. Withdrawal can be so powerful that it makes it extremely difficult to stop taking the drug, including symptoms like: [38]

a. Crippling pain,

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[36] *Id.*

[37] *Id.*

[38] L. San, et al., *Assessment and Management of Opioid Withdrawal Symptoms in Buprenorphine-Dependent Subjects*, 87 British J. of Addiction 1, 55-62 (1992); Kosten, *supra* note 31.

b. Nausea or vomiting,

c. Insomnia,

d. Craving of the drug,

e. Muscle aches/cramps,

f. Diarrhea,

g. Recurrent chills,

h. Tachycardia,

i. Hypertension, and

j. Anxiety and depression

Withdrawal can last for several days to two weeks (except for methadone and buprenorphine withdrawal that typically last longer) and can vary in intensity based on the type, dose and duration of the opioid prescribed.[39]

88. The higher the dose or the greater the intrinsic potency of the opioid administered, the higher the degree of tolerance and of physical dependence, and the more severe the withdrawal syndrome.[40]

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[39] Volkow, *supra* note 25 at 1256 (citing Jennifer Kaufling, et al., *Persistent Adaptations In Afferents To Ventral Tegmental Dopamine Neurons After Opiate Withdrawal*, 35 J. Neuroscience 10290-303 (July 2015), http://www.jneurosci.org/content/35/28/10290; Rita Z. Goldstein and Nora D. Volkow, *Dysfunction Of The Prefrontal Cortex In Addiction: Neuroimaging Findings And Clinical Implications*. 12 Nature Rev. Neuroscience 652-69 (2011)).

[40] Kosten, *supra* note 31; W.B., Cammarano, et al., *Acute Withdrawal Syndrome Related To Administration Of Analgesic And Sedative Medications In Adult Intensive Care Unit*, Critical Care Medicine 26(4):676-684, (Apr. 1998), https://www.ncbi.nlm.nih.gov/pubmed/9559604; *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*, (13th ed.), Chapter 20; M.J. Christie, *Cellular Neuroadaptations To Chronic Opioids: Tolerance, Withdrawal And Addiction*, British Journal of Pharmacology, 2008, https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1038/bjp.2008.100; *The ASAM Principles of Addiction Medicine* (6th ed.); Volkow, *supra* note 25 at 1256 (citing Kaufling, *supra* note 39 and Goldstein *supra* note 39).

89. Tapering off of higher doses of opioids can be very challenging clinically, often resulting in withdrawal and increasing the risk of relapse. Once a patient is exposed to opioids at high doses and for long durations, it is often *very* difficult to remove that patient from opioids.[41] For example, in a recently presented study, of the original 68 patients in the study (51 remained until completion), only 16 patients reduced their opioid dose to below 90 mg daily, and only 4 patients tapered off the drug entirely.[42] Of the original enrolled patients, only 23.5% reduced their dose to what is considered less than high risk and only 5.8% were able to taper completely off of the medications.[43]

90. Tolerance, dependence and withdrawal are serious consequences that are nearly certain with long-term opioid use, and they are not to be minimized.

91. Further, exposing the brain to opioids at a high dose over an extended period of time also seems to alter the underlying brain, leaving it more sensitive to withdrawal and, in some cases, more sensitive to pain. This effect has been termed hyperalgesia.[44]

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[41] Laura Murphy, et al., *Guidance on Opioid Tapering in The Context of Chronic Pain: Evidence Practical Advice and Frequently Asked Questions*, (Feb. 8, 2018), Canada Pharm. J. 151(2), 114–120, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5843113/; Mark Sullivan, et al., *Prescription Opioid Taper Support for Outpatients With Chronic Pain: A Randomized Controlled Trial*,18 J. Pain 3, 308-18, https://www.jpain.org/article/S1526-5900(16)30328-5/abstract; Chantal Berna, *Tapering Long-term Opioid Therapy in Chronic Noncancer Pain*, 90 Mayo Clinic Proc. 6, 828-42 (2015), https://www.ncbi.nlm.nih.gov/pubmed/26046416.

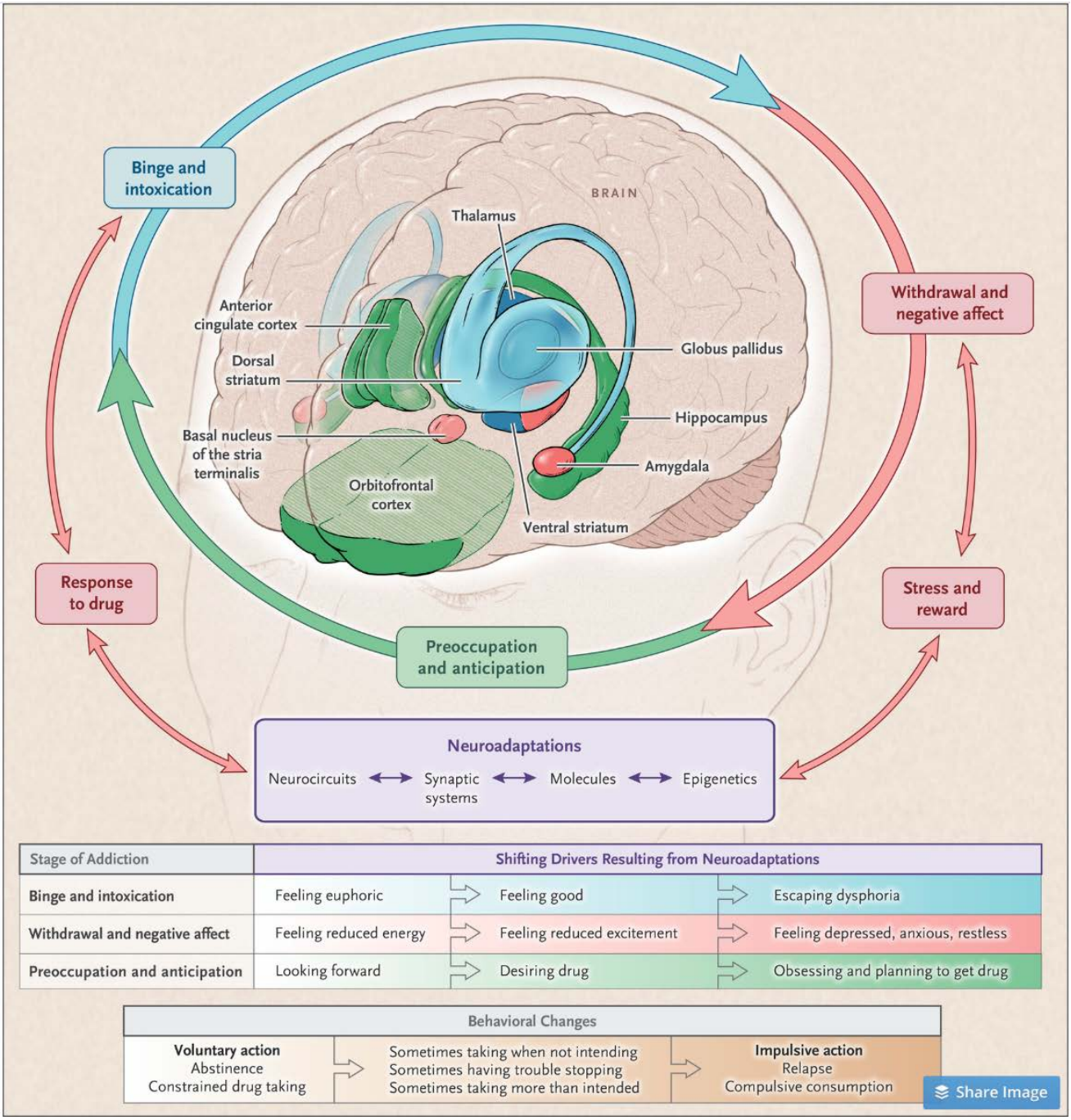
[42] Beth Darnall, et al., *Patient-Centered Prescription Opioid Tapering in Community Outpatients With Chronic Pain*, JAMA (Feb. 19, 2018), https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2672574.

[43] *Id.*

[44] Peggy Compton, et al., *Withdrawal Hyperalgesia After Acute Opioid Physical Dependence in Nonaddicted Humans: A Preliminary Study*, 4 The Journal of Pain 9, 511-519 (2003).

92. In people with addictive disease, withdrawal becomes part of a dangerous cycle that often leads to severe consequences for the person with that disease, including the stages illustrated in the following graphic:[45]

[45] Nora Volkow, et al., *Neurobiologic Advances From the Brain Disease Model of Addiction*, 374 N. Engl. J. Med.1253-1263 (2016), DOI: 10.1056/NEJMra1507771.



93. As more fully discussed below, breaking this cycle is extremely difficult without a proper treatment system.

c. Addictive Disease

94. As discussed in the definition section, Addictive disease is a clinical term that describes alcoholism and drug addiction. The American Society of Addiction Medicine ("ASAM") defines addiction as:[46]

> A primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

95. Addiction to opioids is also referred to as Opioid Use Disorder (OUD). Addiction is best conceptualized not as an abnormality in substance use, but as an abnormality in the brain's response when a person with the disease uses substances as a pathological source of reward or relief. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

96. As also discussed in the definition section, in addition to the ASAM definition of addiction, the APA (American Psychiatric Association) has put forth a series of criteria in the DSM-V for use in diagnosing addiction (OUD), defined as two or more of the following within a 12-month period:[47]

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[46] Definition of Addition, *supra* note 3.

[47] *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.).

a. Using larger amounts of opioids or over a longer period than was intended;

b. Persistent desire to cut down or unsuccessful efforts to control use;

c. Great deal of time spent obtaining, using, or recovering from use;

d. Craving, or a strong desire or urge to use substance;

e. Failure to fulfill major role obligations at work, school, or home due to recurrent opioid use;

f. Continued use despite recurrent or persistent social or interpersonal problems caused or exacerbated by opioid use;

g. Giving up or reducing social, occupational, or recreational activities due to opioid use;

h. Recurrent opioid use in physically hazardous situations;

i. Continued opioid use despite physical or psychological problems caused or exacerbated by its use;

j. Tolerance (marked increase in amount; marked decrease in effect);

k. Withdrawal syndrome as manifested by cessation of opioids or use of opioids (or a closely related substance) to relieve or avoid withdrawal symptoms; and/or Severity of opioid use disorder is categorized as mild (presence of 2-3 symptoms), moderate (4-5 symptoms), or severe (6 or more symptoms).

97. The identifying factors were designed to provide guidance for practitioners to diagnose and treat addiction, and to some extent to clarify severity of the disease state. The criteria do not always provide a bright-line differentiation between dependence, misuse, and addiction and the criteria should not be used as a basis to ignore the many millions of people that

are dependent on opioids (a population who is often unable to be removed from the drugs and needs to be treated for months if not years in order to allow them stop taking the opioid drugs)

98. Development of the disease of addiction in individuals generally occurs as the result of three primary groups of factors:[48]

a. Biology (Genetics);

b. Environment; and

c. Exposure.

99. Susceptibility to addiction differs by person because different people have different vulnerabilities to various genetic, environmental and social factors.[49] In fact, as Volkow points out, "many genetic, environmental and social factors contribute to a person's unique susceptibility to using drugs initially, sustaining drug use, and undergoing the progressive changes in the brain that characterize addiction."[50] According to Volkow, it is estimated that the most severe phenotypic characteristics of addictive disease will develop in 10% of people exposed to addictive drugs like opioids.[51]

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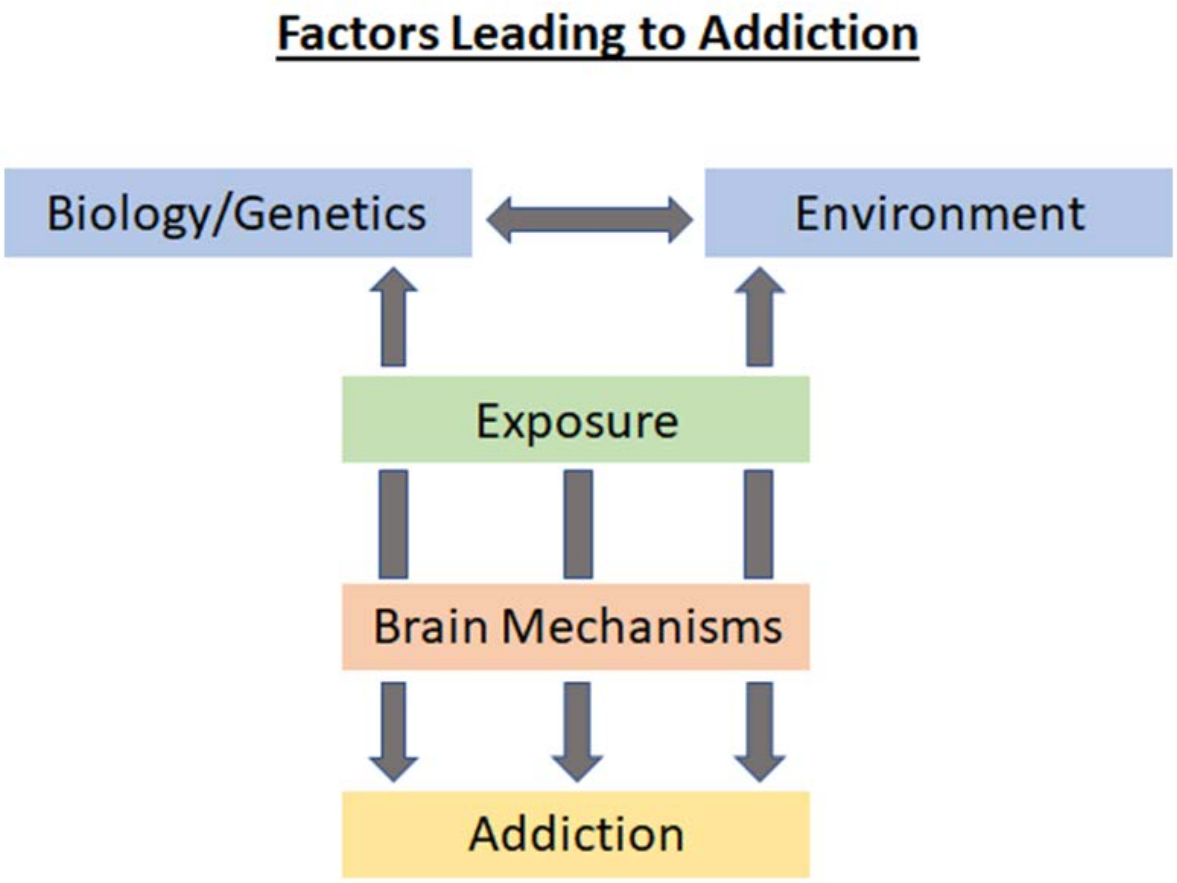
[48] Nora Volkow, M.D., *Drugs, Brains, and Behavior: The Science of Addiction*, NIDA (July 2018), https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction; Mary Jeanne Kreek, et al., *Genes Associated with Addiction*, 5 Neuromolecular Medicine 85 (2004), https://doi.org/10.1385/NMM:5:1:085.

[49] Volkow, *supra* note 48, at 367.

[50] *Id.* (citing Catherine Demers et al., *The Genetics, Neurogenetics and Pharmacogenetics of Addiction*, 1 Current Behavioral Neuroscience Reports 1, 33-44 (2014); Nora Volkow et al., *The Genetics of Addiction*, 131 Human Genetics 6, 773-77 (2012), https://link.springer.com/article/10.1007%2Fs00439-012-1173-3).

[51] *Id.*

100. However, as illustrated in the diagram below, biology and environment do not cause addiction unless patients are exposed to the addictive drugs.[52]



101. Here, and as further explained in *supra* Section J, the epidemic we are experiencing today was a direct result of the massive exposure of a wide swath of the United States to prescription opioids. Exposure to prescription opioids is the key factor. Without exposure to opioids, addiction to opioids cannot develop.

[52] NIH, *Drugs, Brains, and Behavior: The Science of Addiction*, NIDA (July 2018). https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction/drug-misuse-addiction.

102. The Defendants who manufactured, marketed, sold and distributed opioid drugs caused that exposure.

103. While not all people who are exposed to opioids will develop addictive disease, a significant number will. The risk of addiction certainly is not rare when patients are exposed to opioids for long-term use. Studies have shown that between 8 and 12 percent of patients prescribed opioids for long-term use develop a moderate to severe Opioid Use Disorder (approximately 1 in 10).[53] Additionally, those who will develop mild Opioid Use Disorder are roughly two to three times the population of moderate to severe OUD (Vowles cites a misuse rate of 21-29%).[54] Therefore, when opioids are used long-term or to treat chronic pain conditions, the total spectrum of OUD (including mild to severe) that is likely to result is somewhere between 29 to 41%.[55]

104. Who will develop Opioid Use Disorder is impossible to completely and accurately predict; making it even more risky and inappropriate for Defendants to have marketed opioids for a wide swath of the population.[56]

105. It is especially difficult for doctors outside the addiction medicine specialty, who typically have little training regarding addiction, to try to identify the patients who might develop addictive disease prior to prescribing opioids. Therefore, when Defendants' Drugs were

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[53] Kevin Vowles, et al, *Rates of Opioid Misuse, Abuse, and Addiction in Chronic Pain: A Systematic Review and Data Synthesis*, 156 Pain, 569-576 (2015), doi:10.1097/01.j.pain.0000460357.01998.f1.

[54] *Id;* (Vowles' definition of misuse is consistent with DSM-V definition of OUD-mild.).

[55] *Id.*

[56] *Id.* at 1257.

marketed to a wide variety of physician specialties to treat a wide range of conditions using the message that it is relatively straightforward to predict and screen out those who would become addicted is easily done (*see infra* Section IV.H.2.m), that marketing was false, misleading and put patients at risk.

106. What could be predicted, however, was that by exposing a wide population to opioids for long-term use, particularly at high doses, Defendants would cause addiction in a significant portion of people:[57]

C. There Is no Credible Evidence that Opioids Were Suitable to Treat Chronic Pain in Most Patients

107. What is so troubling about the exposure of so many patients to opioids at high doses and for prolonged durations is that there has never been real, credible evidence to support the effectiveness of using opioids long-term to treat chronic pain.

108. Indeed, there is no randomized clinical trial data that has shown efficacy in treating patients with opioids for chronic pain conditions for extended periods of time.[58] In fact, randomized controlled trials have shown that using long-term opioid therapy for chronic pain conditions is *not* superior to non-opioid or placebo.[59] This lack of evidence was summarized in a

[57] *Id.*

[58] Most RCTs were initially less than 12 weeks and there are no RCTs that study patients who took opioids for longer than one year.

[59] Erin Krebs, *Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain*, 319 JAMA 9, 872-882 (2018), doi:10.1001/jama.2018.0899 (2018 randomized trial found that opioids were not superior to non-opioid therapy over a one-year trial period); Jason Busse, *Opioids for Chronic Noncancer Pain A Systematic Review and Meta-analysis*, 320 JAMA 23, 2448-2460 (2018), doi:10.1001/jama.2018.18472) (2018 meta-analysis reporting that there was no Minimally Important Difference in pain reduction or function with opioid therapy compared to either placebo or non-opioid therapy).

recent JAMA meta-analysis and editorial finding that opioids are generally ineffective in the treatment of long-term chronic pain and that there is little evidence for substantial efficacy in chronic pain management.[60]

109. Moreover, as the CDC observed, "[t]he amount of opioids prescribed and sold in the US quadrupled since 1999, but the overall amount of pain reported by Americans hasn't changed."[61] The number of people who have either died or otherwise been harmed by prescription opioids during that same time, however, has risen dramatically.

110. In 2017, the National Academies of Science Engineering and Medicine issued their Consensus Report on "Pain Management and the Opioid Epidemic," which summarized the problem with the wide promotion of opioids to treat chronic pain and for long-term use, stating "data demonstrating benefits of long-term use of opioids to manage chronic, noncancer pain are lacking, while the evidence clearly demonstrates that long-term use of opioids is associated with an increased risk of OUD and overdose as well as a number of other adverse outcomes (*e.g.* cardiovascular events, fractures)."[62]

111. There is no real objective standard or bright line test delineating when opioids are appropriately given for long-term use or to treat chronic conditions. At most, opioids are properly indicated for the short-term treatment of moderate to severe acute pain (e.g. trauma or

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[60] Busse, *supra* note 59.

[61] *CDC Guideline for Prescribing Opioids for Chronic Pain (Factsheet)*, CDC, https://www.cdc.gov/drugoverdose/pdf/guidelines_at-a-glance-a.pdf

[62] National Academies of Science, Engineering and Medicine, *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use* 17 (Phillips, et al. eds., 2017) (hereinafter, "NASEM, *Pain Management and the Opioid Epidemic*").

post-surgical pain); end-of-life pain/hospice care; and cancer pain from active malignant disease. Chronic opioid therapy is not recommended for most common chronic pain conditions (defined as moderate to severe pain lasting beyond 90 days), including low back pain, centralized pain such as fibromyalgia, and headache pain. In less common moderate to severe chronic pain conditions (such as pain from advanced multiple sclerosis, sickle cell disease, pain following spinal cord injury and paraplegia, or post-herpetic neuralgia), which comprise a small percentage of chronic pain patients, opioids may be considered a third-line therapy (taken if other therapies are ineffective or contraindicated).

112. Given the above narrow criteria for indicated chronic pain use, its role as third-line therapy, and the significant risks associated with its use, chronic opioid therapy for persons with chronic pain conditions is, at most, indicated in less than 10% of patients with chronic pain and likely significantly fewer. Among all opioids prescribed for long-term use (i.e. prescriptions written for 90 days, or 30 days with refills, including for acute conditions, this percentage is much smaller. For all proper indications other than hospice care, if prescribed, opioids should be prescribed with the lowest effective dose of preferably immediate-release opioids, taken only when needed and only as long as necessary.

113. Even in the cases where opioids are given to treat chronic conditions there are challenges to determining whether the drugs are actually effective. While some patients report experiencing a benefit from chronic opioid therapy, it is often not possible to differentiate such anecdotal reports of benefit from the effect of each subsequent opioid dose in warding off the symptoms of withdrawal from the previous dose. Therefore, studies that attempt to report on the "benefits" of opioids for chronic pain may be overreporting the alleged "benefit."

D. It is Difficult to Identify the Patients Who Could Benefit from Long-Term Opioid Treatment Without Putting Patients at Risk

114. While there is likely a small percentage of patients who feel they benefit, or do benefit, from opioid treatment, it is difficult to identify those patients prior to initiation of long-term treatment with opioids.

115. There have been no consistent and clear standards, definitions or guidelines for doctors to prospectively identify the small minority of patients who might benefit from long-term opioid treatment for chronic pain and distinguish them from the vast majority of people for whom opioids will not work long-term or those who opioids will trigger addictive disease. The only way to determine who the small population is who may benefit from long-term opioid treatment is retrospective, after the course of treatment has been performed.

116. Evaluating the benefits of long-term opioid treatment retrospectively might be appropriate if there was not a substantial risk to doing so. There is a serious risk of administering opioids to a wide swath of the population, however, as it is impossible to predict with any degree of reasonable certainty which patients will actually benefit, and of those, which patients the treatment will harm.

117. Taking into account these realities, Defendants' promotion of opioids for widespread and long-term use for a wide variety of pain conditions, simply promoted a human experiment, unsupported by scientific data, that put a far larger population at risk than ever should have been exposed to opioids. This has turned out to be a public health disaster and a disaster for communities such as Cuyahoga and Summit Counties.

118. Simply put, because of the lack of benefit, the lack of prospective criteria to identify patients who benefit from long-term opioid treatment and the real risks associated with opioids, these drugs should not be, and never should have been, considered as a first choice in

the management of chronic pain conditions or for long-term use, and in many patients never should have been considered as a choice at all.

E. The Risks of Opioids Have Been Consistent Over Time

119. The very real and serious consequences of opioids have been known for well over one hundred years.

120. Not only is it well known that opioids are highly addictive drugs, but there are many instances in history of increased exposure to opioids from increased use leading to increased abuse and addiction, such as:

i. Early 1800's – Throughout the early nineteenth century, the medical and recreational use of opium grew in England and by 1830, the British dependence on the drug reached all-time highs.

ii. 1861-1865 - During the Civil War, medics use morphine as a battlefield anesthetic. Many soldiers became dependent on and addicted to morphine after the war.

iii. 1898 - Heroin was first produced commercially by the Bayer Company. At the time, heroin was believed to be less habit-forming than morphine, so it was dispensed to individuals who were addicted to morphine. Later, of course, it was discovered that heroin was also highly addictive and, in 1924, the Anti-Heroin Act banned the production and sale of heroin in the United States.

iv. During the 1970s the United States saw a period of addiction to heroin among US Military in the United States following the Vietnam war after troops had been exposed to heroin in Vietnam.

121. Of course, as set forth in further detail in *supra Sections* IV.J and I.A.1 in this report, there is no better evidence of the terrible results of exposing a significant population to opioids than the ongoing epidemic in this country.

122. Not only did history and experience make clear that it was unwise to expose large numbers of people to opioids, especially over long durations and in high doses, but science identified substantial risks to doing so.

123. Indeed, long before the recent sea change in American opioid prescribing started in early to mid-1990s, studies had observed significant rates of opioid addiction in opioid users.[63]

124. Particularly, studies have repeatedly shown substantial evidence of addiction, misuse and physiologic dependence when opioids were used long-term to treat chronic pain conditions:

i. Between 8 and 12 percent of patients prescribed chronic opioids develop a moderate to severe Opioid Use Disorder (approximately 1 in 10).[64]

ii. Roughly 21% to 29% of patients prescribed opioids for chronic pain misuse them (this equates to a mild Opioid Use Disorder under DSM-V)[65]

[63] *See e.g.*, Kolb, Mental Hyg, (1925); Rayport JAMA (1954); Fishbain (1992), Clin J Pain 8:77-85 (up to 18.9%); Turner, Pain 1982; 12:357-363 (16%); Evans, Anasthesia 1981; 36:597-602 (16% as cited by Fishbain, 1992); Katon, Am J Psychiatry 1985; 142:1156-60 (18.9%); Bouckoms, Ann Clin Psychiatry 1992; 8:185-92 (24%); Maruta, Mayo Clin Proc 1979; 54:241-244 (24%).

[64] Vowles, *supra* note 53.

[65] *Id.*

iii. 43% of opioid-treated chronic nonterminal pain patients in one pain clinic were judged "problematic," meaning that the patients had either positive urine toxicology or one or more aberrant drug-taking behaviors.[66]

iv. 45% of patients on chronic opioid therapy in one pain clinic were found to have abnormal urine screens[67].

b. 24% of claims for patients on chronic opioid therapy in a large commercial insurance database contained an indicator of possible current opioid misuse.[68]

c. 41.3% lifetime prevalence of opioid use disorder in chronic pain patients treated long-term with opioids (28.1% mild and 13.2% moderate to severe)[69]

d. 34% of people taking prescription painkillers for longer than 2 months believe that they are addicted to or dependent on the medication, according to a 2016 survey of over 800 individuals, weighted to match the national adult population demographically.[70]

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[66] Nathanial Katz, et al., *Behavioral Monitoring and Urine Toxicology Testing in Patients Receiving Long-Term Opioid Therapy*, 97 Anesth. Analg. 1097-102 (2003).

[67] Edward Michna, et al., *Urine Toxicology Screening Among Chronic Pain Patients on Opioid Therapy: Frequency and Predictability of Abnormal Findings*, 23 The Clinical J. of Pain, 2, 173-79 (2007).

[68] M.D. Sullivan, et al., *Risks For Possible And Probable Opioid Misuse Among Recipients Of Chronic Opioid Therapy In Commercial And Medicaid Insurance Plans: The TROUP Study*, 150 Pain 2, 332-39 (2010).

[69] Joseph Boscarino, et al., *Prevalence Of Prescription Opioid-Use Disorder Among Chronic Pain Patients: Comparison Of The DSM-5 Vs. DSM-4 Diagnostic Criteria*. 30 J. Addictive Diseases 3, 185-94 (2011).

[70] Bianca DiJulio, et al., *The Washington Post/Kaiser Family Foundation Survey of Long-Term Prescription Painkiller Users and Their Household Members*, (Dec. 2016), http://files.kff.org/attachment/Survey-of-Long-Term-Prescription-Painkiller-Users-and-Their-Household-Members.

e. According to the American Society of Addiction Medicine's Handbook on Pain and Addiction, "the preponderance of estimates [regarding the prevalence of opioid use disorder] are in the range of 20-25%."[71]

125. Patients with addictive disease are over-represented in chronic pain patient populations, especially those chronic pain populations who are on long-term opioids. Not only did Defendants expose the American population to the risks associated with prescription opioids, but they exposed a highly vulnerable population to these risks. Worse yet, they did so at high doses and for long durations, virtually ensuring that addiction, misuse, diversion and physiologic dependence would ensue.

F. Prior to the 1990s, prescribing was conservative.

126. Because of the well-known risks of treatment using opioids, historically opioids were used quite conservatively for pain management in general, and for chronic pain management in particular.

127. Even as recently as the late 1980s, opioids were virtually never provided for chronic pain, and were primarily reserved for acute pain and malignant palliative care type pain.

128. This was based on valid concerns regarding the risks of opioids, including that of addiction, accidental overdose, physical dependence and withdrawal.

129. The baseline for opioid prescribing in American medical practice should be considered to be in the late 1970s through the late 1980s, rather than any time afterwards.

[71] American Society of Addiction Medicine, *Handbook on Pain and Addiction* (Illene R. Robeck, et al. eds., 2018).

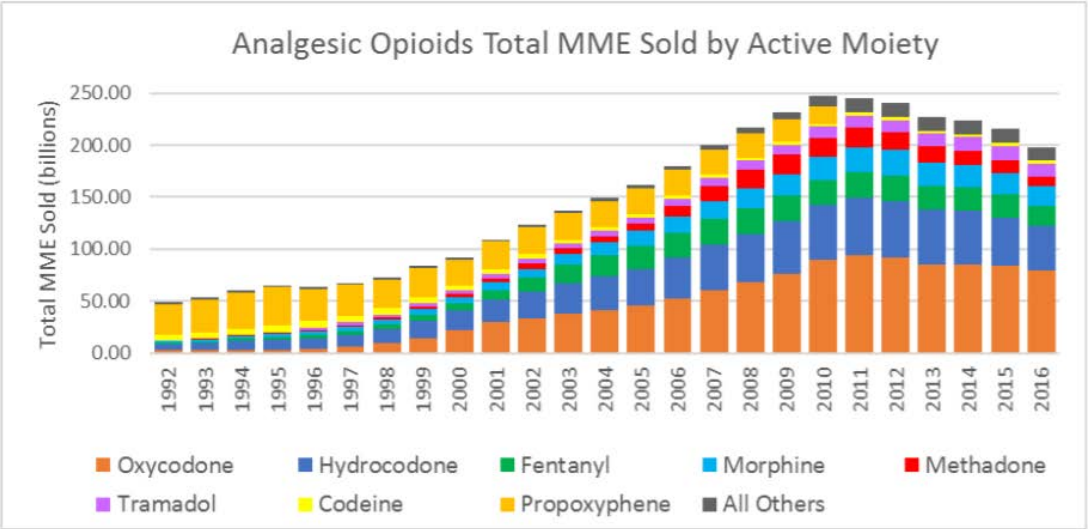
G. Starting in the 1990s- Defendants Exposed a Population to Prescription Opioids in unprecedented amounts, doses and durations

130. In the early 1990s, pharmaceutical companies who were developing newer forms of opioids having higher potency and newer delivery systems, and certain palliative care physicians who were quite comfortable with the prescribing of opioids in end-of-life patient management, many of whom were funded by various pharmaceutical companies, began to advocate for a major change in medical practice: the long-term prescribing of moderate to high doses of opioids on a daily basis in the management of chronic pain and a wide variety of pain conditions.

131. As a result of this sea change in the use of opioids, a dramatically increased population of people were exposed to prescription opioids throughout the United States and in Ohio.[72]

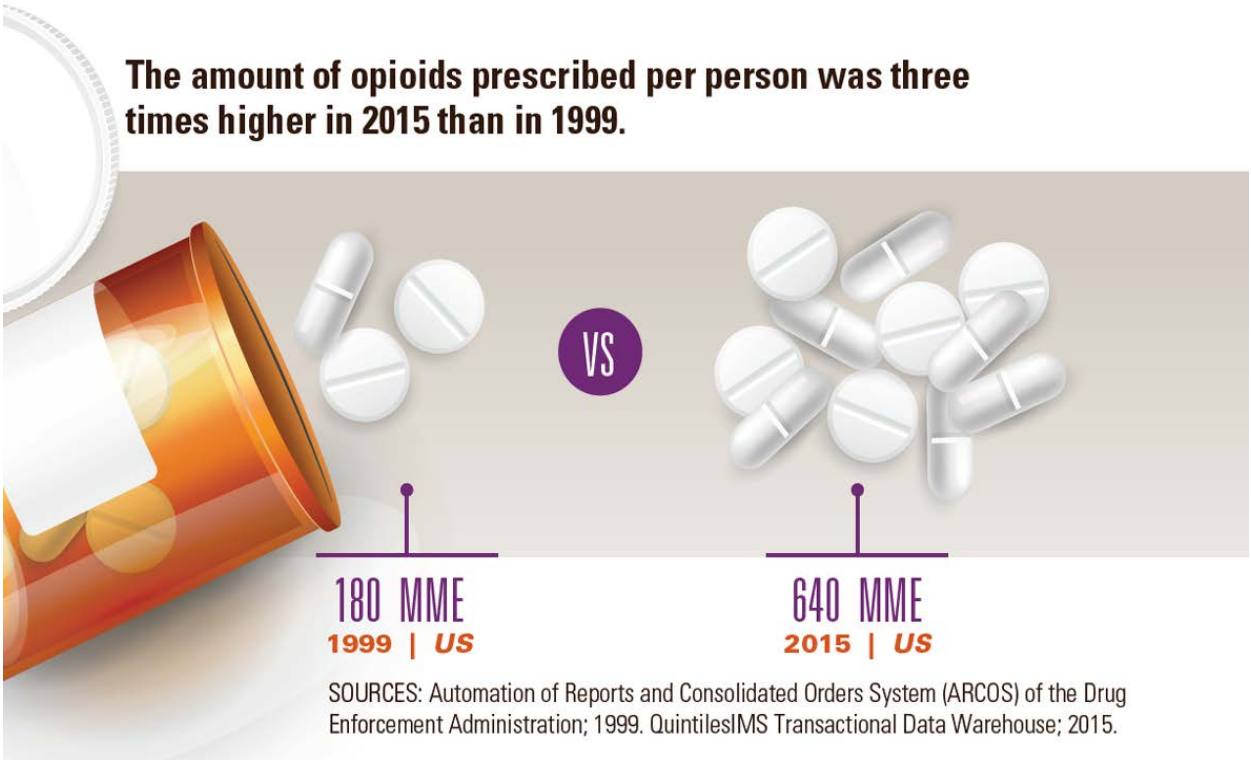
[72] *FDA Analysis of Long-Term Trends in Prescription Opioid Analgesic Products: Quantity, Sales, and Price Trends*, FDA (Mar. 1, 2018), https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM598899.pdf; *Ohio Opioid Summary*, NIDA (Feb. 2018), https://www.drugabuse.gov/drugs-abuse/opioids/opioid-summaries-by-state/ohio-opioid-summary.

Figure 2: Total MMEs sold for aggregate opioid analgesic market – by active moiety



132. Not only did the number of opioids prescribed increase, but the amounts prescribed per person (as measured in MMEs) in the United States was 3.5 times higher in 2015 than in 1999.[73]

[73] CDC, *Opioid Prescribing (Graphic: Where You Live Matters)*, CDC Vital Signs, (July 6, 2017), https://www.cdc.gov/vitalsigns/opioids/infographic.html#graphic-a (citing Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration; 1999. QuintilesIMS Transactional Data Warehouse; 2015).



133. The duration of prescriptions also increased, causing a perfect storm for dependence, misuse and addiction.[74]

134. In short, communities in America, including in Ohio and in the Summit and Cuyahoga communities, were exposed to prescription opioids in unprecedented numbers, doses and durations. That exposure was a key component to the recent, massive increase of opioid addiction, dependence, misuse, and diversion to illicit use in the United States, in Ohio and in Summit and Cuyahoga Counties.

135. There was no clinical reason for this avalanche of pills. In fact, there was no reason for the baseline of opioid prescribing to have changed so dramatically from the baseline

[74] CDC, *Opioid Prescribing: Where You Live Matters*, CDC Vital Signs, (July 6, 2017), https://www.cdc.gov/vitalsigns/opioids/index.html; Denise Boudreau, et al. *Trends In Long-Term Opioid Therapy For Chronic Non-Cancer Pain*, 18 Pharmacoepidemiology Drug Safety 1166–75 (2009); Michael Von Korff, et al, *De Facto Long-Term Opioid Therapy For Noncancer Pain*, 24 The Clinical J. of Pain 521–7 (2008).

of the 1970s and 1980s ("the Baseline Era"). The amount of pain in the United States had not dramatically changed from the Baseline Era. Products like Oxycontin and other of the Defendants' Drugs contained the same active pharmaceutical ingredients as the opioids that had been used in the 1970s, 1980s and 1990s, including ingredients like oxycodone, hydrocodone and oxymorphone that were in earlier products like Percocet, Vicodin and morphine.

136. What did change is that the pharmaceutical industry, along with key opinion leaders and professional societies funded by the drug companies, decided to promote using opioids for long-term chronic pain management by telling the medical community and patients, for example, that (1) the Defendants' Drugs were different and less addictive than opioids previously used to treat pain (2) concerns about addiction risk had been overblown, and (3) being in true pain insulated patients from the risk of addiction. *See* Section IV.H below.

137. What did change was the dramatic increase in the supply of opioids to Ohio and the United States of a highly addictive and highly abusable Schedule II narcotic. *See supra* paragraph 132.

138. In fact, one way to illustrate how the sea change in sales and supply was driven not by clinical forces is that the United States accounts for almost 5% of the world's population but consumes a large percent of the world's opioids.[75] Indeed, in 2016, the International Narcotics Control Board reported that the United States accounted for over 99 per cent of the

[75] International Narcotics Control Board (INCB), *Comments On The Reported Statistics On Narcotic Drugs*, International Narcotics Control Board (2017), https://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2017/7 _Part_2_ comments_E.pdf.

global consumption of hydrocodone and 72.9 per cent of the global consumption of oxycodone.[76]

139. There is no reason Americans would have dramatically higher incidence of pain that can explain this discrepancy. And United States was not the only country in which opioids can be used to treat chronic pain.[77] Further, as reported by the CDC, after two decades of pouring opioids into the United States, there has been no appreciable change in the incidence of pain in the United States.[78]

140. Even if one accepts that pain was "undertreated," as the pain movement of the 1990s and 2000s suggested, Defendants had not invented a new "cure" for pain in the form of Defendants' Drugs. Indeed, there was no clinical reason that these drugs should have been used in a dramatically different way than opioids were used in clinical practice in the Baseline Era.

H. The Marketing Messages Used to Create That Sea Change in Medical Practice

141. I have been provided with the Second Amended Complaints ("Complaint(s)") in which Summit and Cuyahoga Counties state that Defendants caused the dramatic exposure to prescription opioids through their false and misleading marketing practices and unlawful distribution practices.

142. I have been provided with a list of those messages, which I understand that Plaintiffs' experts, including Dr. Perri, have identified as common themes and messages that Defendants used in marketing (Schedule 5 to my report). I have been asked to comment on the

[76] *Id.*

[77] *Id.*

[78] CDC Guideline, *supra* note 1.

accuracy of the common themes and messages and the appropriateness for use in widely marketing opioids. My opinions on those common themes and messages are as follows. Much of the basis for these opinions has already been set forth in *supra* Sections IV.A- IV.G. Therefore, instead of reproducing those Sections here, I will simply refer back to those Sections where needed.

1. Common Marketing Themes

a. Theme One: Dependence, Tolerance, Addiction and Withdrawal Should not be a Concern in Prescribing Opioids

143. For the reasons discussed in the previous sections, and in the following section addressing common messages, this theme downplaying the risk of prescription opioids to reverse years of conservative prescribing practices and habits was false, misleading and had devastating consequences for patients and communities. Opioids as a drug class are highly addictive and have a high potential for abuse and diversion. Defendants' Drugs were no exception. The idea that the inherent risks opioids pose, are substantially mitigated because they are being administered pursuant to a prescription, particularly at high doses for long duration, is pure fantasy without meaningful scientific support. And when combined with other false concepts, such as that prescribers can with little risk titrate up to address tolerance, or that traditional warning signs of addiction were likely pseudo-addiction and really signs of untreated pain, it resulted in dramatically increased opioid prescribing that exposed patients, families and communities to massive quantities of opioids, thus laying the foundation of the opioid epidemic we have today. The truth is that dependence, tolerance and addiction should be primary concerns that prescribers need to understand and be alert for, particularly when prescribing opioids long-term or at high doses. Any messages to the contrary that Defendants delivered in sale, marketing, promotion, or distribution of the Defendant's drugs is simply untrue.

b. Theme Two: Opioids are effective for, and improve functioning in, patients taking them for long-term and chronic use

144. For the reasons discussed in the previous sections, and in the following section addressing common messages, this was never true, particularly as a general rule. As a general rule, exposing patients long-term to opioids, particularly at high-doses, is dangerous and increases the risk of dependence or addiction. As discussed above and in the sections below, this and other basic principles about the risks of opioids were long understood, and there was no scientific breakthrough demonstrating that our prior understanding and experience with opioids was wrong or that prescribing them for long-term use to treat most chronic pain patients was appropriate.

c. Theme Three: Opioids should be first-line therapy for pain.

145. This is not, and never was, true. Even in the context of acute, cancer, or end-of-life pain, opioids should not be a first option if the pain is mild and can be controlled with non-opioid analgesics. And it is never true in the case of commonly encountered chronic pain conditions, such as back pain. As stated above, at most, opioids are properly indicated for the short-term treatment of moderate to severe acute pain (e.g. trauma or post-surgical pain); end-of-life pain/hospice care; and cancer pain from active malignant disease. Chronic opioid therapy is not recommended for most common chronic pain conditions (defined as moderate to severe pain lasting beyond 90 days), including low back pain, centralized pain such as fibromyalgia, and headache pain. In less common moderate to severe chronic pain conditions (such as pain from advanced multiple sclerosis, sickle cell disease, pain following spinal cord injury and paraplegia, or post-herpetic neuralgia), which comprise a small percentage of chronic pain patients, opioids may be considered a third-line therapy (taken if other therapies are ineffective or contraindicated). For all proper indications other than hospice care, if prescribed, opioids should

be prescribed with the lowest effective dose of preferably immediate-release opioids, taken only when needed and only as long as necessary.

2. Common Messages

a. Message 1: Extended release drugs and/or q12 dosing had fewer peaks and valleys and less chance of addiction and abuse.

146. This message is false for at least the following reasons and for the reasons stated in *supra* Section IV.H.1.a.

147. Extended release or long acting opioids (ER/LA opioids) provide 12 hour or 24 hour or 72-hour dosing, the point of which is to try and increase convenience for patients by reducing the number of doses they have to take during a day.

148. There is no evidence that ER/LA opioids decrease the risk of addiction or dependence. The little evidence there is regarding their abuse potential ignored how the extended release aspect was easily defeated by, for example, crushing or chewing.

149. In reality, as we have now seen, even though marketed as different and safer, extended release drugs were no different in terms of their ability to cause dependence, addiction, overdose and death, and in fact were worse.

150. Extended release opioids contain the same active ingredients that have been known to be addictive for decades (if not much longer). (*See supra* Section IV.E) In fact, Defendant Purdue admitted that its statements to prescribers that OxyContin, an ER/LA opioid, caused less euphoria and had less addiction and abuse potential than immediate release opioids were false and misleading.[79]

[79] *See, e.g.*, Agreed Statement of Facts, Case No. Case 1:07-cr-00029-JPJ (W.D. Va.), Document 5-2, https://www.documentcloud.org/documents/279028-purdue-guilty-plea.

151. Additionally, the abuse potential is first and foremost related to the intrinsic dopamine surge of the drug, which is present in all Schedule II opioid narcotics. *See* Sections IV.B.1 and IV.B.3. Indeed, certain opioid abusers and opioid addicted individuals demonstrated a willingness to illicitly buy or otherwise go to great lengths to seek prescribed ER/LA opioids. For example, Oxycontin, the first of the extended release opioids to be widely promoted, was widely abused and caused addiction and death of many of the people who took the drug.

152. Secondly, ER/LA opioids provide high sustained blood levels of opioids to the brain, and as such maximize the possibility of developing physical dependence and withdrawal as discussed in *supra* Section IV.B.3.

153. Thirdly, these ER/LA opioids typically had very large doses or high potency of morphine equivalent. One of the principle characteristics of an opioid that drives its likelihood of abuse/physical dependence/addiction is the potency of that drug and the amount of the potent drug in the specific preparation; thus, these ER/LA formulations, far from decreasing the risk of addiction and abuse, increased the risk of abuse, physical dependence, withdrawal and addiction. *See supra* Section IV.B.3.

154. Although OxyContin's initial prescribing information included the statement that '[d]elayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug,"[80] that language was removed in 2001.[81] In recommending the removal of that language, FDA officials contrasted the "experience with the product on the market" with the

[80] PPLPC016000029745.

[81] PDD1501610836.

abuse sections of the drug label, and recommended adding a black box warning.[82] OxyContin did add a box warning, which stated "[o]xycodone can be abused in a manner similar to other opioid agonists, legal or illicit."[83]

155. Language in OxyContin's label that said "development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare" was removed in 2006.[84]

156. Purdue pled guilty to felony misbranding for telling prescribers that its extended-release opioid was less addictive and less subject to abuse than immediate release opioids.[85] In entering into this plea, Purdue agreed that the "opioid effects" of OxyContin and immediate-release oxycodone would be similar were false.[86] It further agreed that statements that OxyContin "did not cause a 'buzz' or euphoria, caused less euphoria, had less addiction potential, had less abuse potential, was less likely to be diverted than immediate-release opioids, and could be used to 'weed out' addicts and drug seekers" were false.[87]

157. Other extended release opioids are no different and any efforts to market these drugs as safer or having lower abuse potential was similarly untrue and/or misleading.

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[82] PURCHI-000675080.

[83] Agreed Statement of Facts, *supra* note 79.

[84] PURCHI-000813280.

[85] Agreed Statement of Facts, *supra* note 79.

[86] *Id.* ¶ 16(a).

[87] *Id.* ¶ 43.

b. Message 2: "Abuse deterrent formulations" deter abuse

158. Defendants Purdue and Endo marketed and sold several Drugs that they marketed as "abuse deterrent" starting in 2010 (Purdue) and 2011 (Endo).[88]

159. There is little evidence, however, that so called "abuse deterrent" drugs deter abuse and this message is misleading to the extent it was delivered to convince doctors that so-called "abuse deterrent formulations" were safer to prescribe.

160. So-called "abuse deterrent formulations" are more aptly described as tamper resistant, and thus do nothing to stop abuse by swallowing these prescription opioids orally without crushing, snorting or injecting. Indeed, many people who abuse prescription opioids do not initiate the abuse of the drug by crushing, snorting or injecting and, therefore, the tamper resistant properties do nothing to "deter" most of the people abusing the drug.[89]

161. Also, "abuse deterrent formulations" do not always work as deterrents since abusers and those with addiction work quite hard to get around the deterrent – and often are successful.[90] Individuals intent on abusing opioids, and especially those who are addicted to opioids, are more than willing to "put-up" with truly deterrent formulations in order to gain or maintain longitudinal access to them.[91]

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[88] Purdue could not market OxyContin as abuse-deterrent until a 2013 label change, however.

[89] Pradip Muhuri, et al., *Associations of Nonmedical Pain Reliever Use and Initiation of Heroin Use In The United States*, CBHSQ Data Review (August 2013), https://www.samhsa.gov /data/sites/default/files/DR006/DR006/nonmedical-pain-reliever-use-2013.htm.

[90] Theodore Cicero, et al., *Abuse-Deterrent Formulations and the Prescription Opioid Abuse Epidemic in the United States: Lessons Learned From OxyContin*, 72 JAMA Psychiatry 5, 424–430 (2015).

[91] M. K. Romach, et al., *Update on Tamper-Resistant Drug Formulations*, 130 Drug and Alcohol Dependence (1-3), 13-23.

162. Further, once people are dependent on or addicted to opioids, they do not simply stop taking the drug because they cannot crush it easily. Indeed, as fully described above, that is difficult if not impossible for people who will suffer withdrawal or who have opioid use disorder to do. Instead, people simply continued orally taking the pills or switched to illicit drugs like fentanyl and carfentanil. Indeed, the introduction of reformulated OxyContin and the removal of generic equivalents of older OxyContin shifted the drug of choice for dedicated abusers or those who were addicted to opioid to other drugs, including illicit fentanyl.[92]

c. Message 4: "Abuse deterrent formulations" are safer than non-abuse deterrent formulations

163. While abuse deterrent formulations may deter tampering by crushing, for example, that does not make them "safer" than non-abuse deterrent formulation. Again, the majority of people who abuse prescription opioids do not do so by snorting or IV injection.[93] Further, prescribing a patient an "abuse deterrent" formulation presents the same risks of addiction or dependence as a non-abuse deterrent formulation. Thus, marketing these Drugs as "abuse deterrent" to imply that they were less prone to abuse or less addictive improperly put prescribers at ease that the ADF Drugs were safer than they actually were, resulting in continued prescribing at high doses and potencies.[94]

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[92] *See* William N. Evans, et al., *How the Reformulation of OxyContin Ignited the Heroin Epidemic*, Review of Economics and Statistics (2018); David Powell, et al., *A Transitioning Epidemic: How The Opioid Crisis Is Driving The Rise In Hepatitis C*, 38 Health Affairs 2, 287-294 (2019).

[93] Muhuri, *supra* note 89.

[94] Bucher Bartelson, et al., *Changes in Misuse and Abuse of Prescription Opioids Following Implementation of Extended-Release and Long-Acting Opioid Analgesic Risk Evaluation and Mitigation Strategy*, 26 Pharmacoepidemiology & Drug Safety 9, 1061–70 (2017).

164. Further, the FDA denied Purdue's supplemental New Drug Application to add language stating that "OxyContin has abuse-deterrent characteristics that result in decreased abuse, overdoses, and deaths in the community setting via injecting, snorting, and to a lesser extent via oral abuse compared to levels that occurred when Oxycontin was available only in a formulation without abuse deterrent properties."[95]

d. Message 5: Concerns about Addictive Nature of Opioids Had been Overblown

165. As fully outlined in *supra* Section IV.B, the risks of addiction to opioids are significant, and were not exaggerated. It was utterly false to suggest otherwise and suggestions of this kind lead to the crisis we see today.

166. Indeed, as outlined in *supra* Section IV.E, the addictive nature of opioids has been clear in the West for over one hundred years. Opioids (other than tramadol, codeine and buprenorphine) are all now Schedule II narcotics – and with the exception of hydrocodone combination products, have *always* been Schedule II narcotics – which by definition are highly addictive. Any statement or suggestion that the abuse and addiction potential of opioids had been exaggerated was false and is false.[96] (*See supra* Section IV.D.) Indeed, when Purdue pled guilty to felony misbranding of OxyContin, Purdue agreed that its statements suggesting that OxyContin had less abuse or addiction potential than immediate release opioids were false and

[95] PPLPC002000287252, at 278.

[96] The reason why hydrocodone was originally classified as Schedule III from the time the CSA was enacted in 1970 until recently is that when the CSA was enacted the primary formulation of hydrocodone on the market was a cough syrup – thus better fitting the class of a Schedule III opioid. During the current opioid epidemic, it became clear that hydrocodone in the pill form was frequently diverted and abused, and it was subsequently re-classified in 2014 as a Schedule II narcotic. Sharon Walsh, et al., *The Relative Abuse Liability Of Oral Oxycodone, Hydrocodone And Hydromorphone Assessed In Prescription Opioid Abusers*, 98 Drug And Alcohol Dependence 3, 191–202 (2008).

were intended to deceive physicians and the public.[97] All similar claims by Defendants in marketing were just as false.

167. In fact, Defendant Mallinckrodt, knew that addiction was real. In internal communications, sales executives acknowledged that people were addicted:[98]

From: Steven J. Cochrane [mailto:steve@keysourcemedical.com]
Sent: Tuesday, January 27, 2009 11:08 AM
To: Borelli, Victor
Subject: Re: Oxy 30

Keep 'em comin'! Flyin' out of here. Its like people are addicted to these things or something. Oh, wait, people are...

Thank you,
Steve

Steven J. Cochrane
VP, Purchasing
KeySource Medical, Inc.
An **Inc. 500** *Company*

e-mail Steve@KeySourceMedical.com
direct tel 1-866-371-0408
cell 1-516-510-6582

And joked about continuing to sell their opioid product to those who were addicted:

[97] Agreed Statement of Facts, *supra* note 79.

[98] MNK-T1-0000559532_native.pdf.

To: Steven J. Cochrane[steve@keysourcemedical.com]
From: Borelli, Victor
Sent: Tue 1/27/2009 4:12:08 PM (UTC)
Subject: RE: Oxy 30

Just like Doritos

keep eating, we'll make more.

Victor M. Borelli

National Account Manager, Retail
Covidien
Mallinckrodt Pharmaceutical Generics
O:410.308.0633
F:410.308.0634
C:443.204.7914
email: victor.borelli@covidien.com
www.covidien.com

168. Not only were claims about addiction risk being overstated false, but Defendants like Mallinckrodt were aware of the falsity and just kept selling.

e. Message 6: Science was now showing that opioids were not as addictive as once thought.

169. This message is false and totally contradicted by scientific information. (*See supra* Section IV.E*)* Science did not evolve in the 1990s or 2000s to show Defendants' Drugs, or opioids in general, to be less addictive. In fact, there is, and always has been, a clear epidemiologic relationship between escalations in prescribing (and hence exposure and access in any given community) and the diversion, abuse, addiction, seeking of addiction treatment and

fatal overdose on prescription opioids.[99] Purdue's Dr. Wright testified that "the more prescription drugs you had in the marketplace the more drug abuse cases you would have."[100]

170. As fully set forth above, opioids are and always have been addictive Schedule II narcotics. There was no science to support statements by the Defendants that prior understandings of the risks of prescription opioids was wrong or ill-advised. *(See supra* Section IV.E.*)* For example, Purdue's corporate witness testified that Purdue never studied the risk of iatrogenic addiction to the original formulation of OxyContin.[101]

f. Message 7: True patients in pain do not become addicted to opioids – pain protects against addiction

171. As set in *supra* Section IV.C, this message is totally false. There was never any evidence to promote this misconception and in fact substantial evidence that patients given opioids for pain became addicted to and severely dependent on opioids. (*See supra* Section IV.E.) The message that "true pain" protects against addiction to opioids, is especially insidious because it implies: 1) that there is little need to screen for addictive disease, 2) little reason to use addictive disease as a contraindication to avoid long-term / high dose / out-patient provision of opioids, and 3) if there was evidence of addictive behavior, it was either misperceived (see "pseudo-addiction" below) or it was the patient's fault for faking pain.

[99] Laxmaiah Manchikanti, M. D., et al., *Opioid Epidemic In The United States*, 15 Pain Physician, 2150-1149 (2012).

[100] Wright Dep. Tr. 227:15-19, Dec. 19, 2018.

[101] Fanelli Dep. Tr. 134:10-136:7, Dec. 6, 2018.

172. This myth was – and is – an absolute disaster in clinical practice and has contributed to hundreds of thousands of destroyed lives and tens to hundreds of thousands of fatal overdoses.

g. Message 8: Signs of addiction as symptoms of undertreated pain or "pseudoaddiction"

173. No data or science supported this concept.[102] Coining the term "pseudo-addiction," and then introducing it into the literature and into mainstream medical practice without controlled studies about the prevalence, or even existence, of this "phenomena" was actually "pseudo-science" and very dangerous. (*See supra* Section IV.B.3.c.)

174. This false concept was responsible for treating patients exhibiting potential signs of addiction with exactly what was most dangerous to them: giving them more of the opioid drug they were addicted to or dependent on.[103]

h. Message 9: Problems only occur when opioids are abused or used illegally - addicts are bad people who knowingly abused the drugs, not good people who were seeking treatment for legitimate ailments.

175. As set forth above *in supra* Section IV.B.3 the vast majority of people who abuse opioids often started with prescription. The part of this population who fall into non-medical use, do so not because of a moral failing, but because they were exposed to these highly addictive narcotics and have been dependent on the drugs or addicted to them. As explained in

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[102] Marion Greene, et al., *Pseudoaddiction: Fact or Fiction? An Investigation of The Medical Literature*, 2 Current Addiction Reports 4, 310-17 (2015).

Kirsten Bell, & Amy Salmon, *Pain, Physical Dependence And Pseudoaddiction: Redefining Addiction For 'Nice' People?*,20 Int'l J. of Drug Pol'y, 2,170-178 (2009).

[103] Russell Portenoy Dep. Tr. 217:7-291:21 ("[D]eath could occur if the dose is increased and the patient is in an addictive pattern of abuse, yes.").

supra Section IV.B.3 patients who take opioids as prescribed become almost immediately physically dependent on the drugs, increasingly so at higher doses and for longer durations. As described, in *supra* Section IV.B.3.b it is the often the powerful desire to avoid withdrawal after becoming physically dependent that often drives patients to misuse medications or into taking illegal drugs if their source of medication is cut off. As we have seen acutely in this opioid crisis, patients from all walks of life have become dependent on and addicted to opioids and have die from opioid overdoses. Tragically, people 18-25 years old have been the most significantly affected age group. (*See supra* Section IV.I.10.266.) Addiction is not a choice, it is a disease.[104]

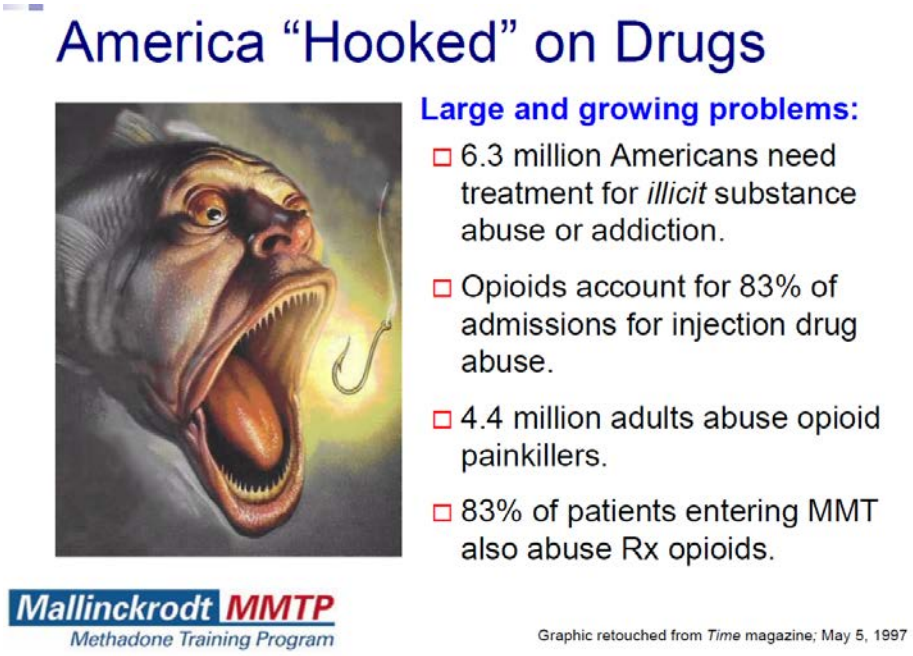
176. Certain defendants such as Mallinckrodt who also sold drugs like methadone to treat addiction acknowledged many of these serious risks in internal training documents. For example, one Mallinckrodt presentation on its methadone product notes how addiction is an involuntary "disease" that disconnects judgment and control functions; thus "patients cannot simply think their way out of addiction."[105] Another Mallinckrodt presentation about its methadone product stresses how "opioid addiction is a large and growing problem in the U.S.," and that it is essential to overcome the "stigma, prejudice, and misunderstandings" surrounding addiction because it is "a chronic, relapsing brain disorder – a disease."[106] Slides from Mallinckrodt's 2004 Methadone Training Program Presentation, "Understanding Addiction: The

[104] *See* Definition of Addition, *supra* note 3.

[105] Mallinckrodt presentation entitled "The Addicted Brain: A Disease Perspective," at 50 (MNK-T1_0001256480).

[106] Mallinckrodt presentation entitled "Understanding Addiction: The Great Brain Robbery," at 5 and 30 (MNK-T1_0001332076).

Great Brain Robbery" discuss how opioids hijack the brain and leave people powerless who become addicted:[107]



[107] *Id.*

People Have Choices *(Initially)*

- Addiction begins as a voluntary act of drug (or alcohol) taking.
- After repeated use, drugs take control; person is transformed.
- Result is a chronic, relapsing brain disorder – "drug addiction."

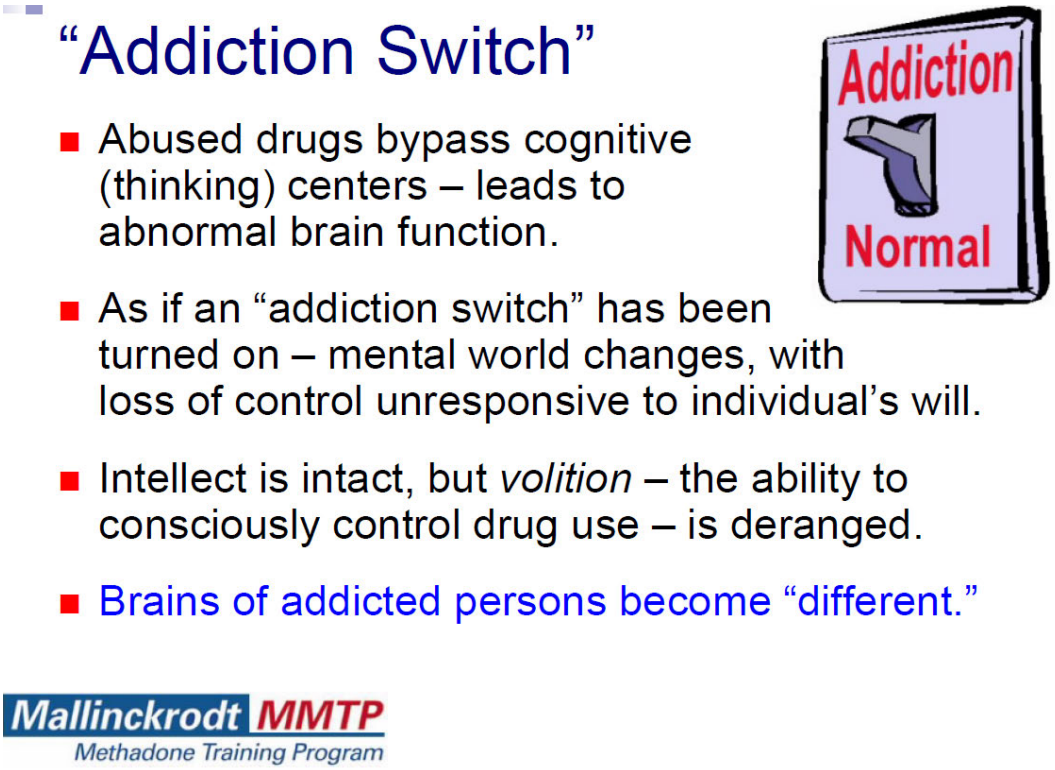
Mallinckrodt MMTP
Methadone Training Program

Drawing courtesy of David Sinclair, PhD; used with permission.

It's All About Dopamine

- Dopamine regulates mood/emotions.
- Responsible for motivation, "natural rewards."
- Addictive drugs stimulate dopamine in brain pathways associated with "reward."
- In addiction, dopamine system becomes dysfunctional…
  - more drug needed.
  - loss of control over drug use.

Mallinckrodt MMTP
Methadone Training Program



177. To suggest that addiction is a choice or that the real risks of opioids exists in some far-off, undefined population of "bad people" or "abusers" is utterly false and is a myth that perpetuated the continued flood of opioids into the United States and the consequent harm we have seen in the current opioid epidemic.

i. <u>Message 10: If taken as prescribed, risk is almost nonexistent.</u>

178. This is also not true and never was true. As Defendant Purdue admitted in its guilty plea, statements to physicians and the public that extended release opioid formulations had less addiction and abuse potential if taken as prescribed than immediate release opioids was false, misleading and intended to deceive.[108]

[108] *See* Agreed Statement of Facts, *supra* note 79.

179. Controlled drugs are prescription drugs that require a DEA number to be prescribed because they are dangerous drugs (i.e. all prescription drugs are dangerous drugs and thus not over the counter) that have abuse and addictive potential (and therefore are controlled drugs). As set forth in *supra* Section IV.E risk is present because opioids are dangerous drugs. That risk increased by Defendants' advocacy for long-term, high dose opioid use and by telling prescribers that abuse deterrence reduced the risk of addiction and abuse when it did not; and that patients with true pain would not become addicted (which also was not true). *See supra* Sections IV.D and IV.E.

180. There is also substantial risk from long-term opioid use apart from abuse or addiction. As outlined in *supra* Section IV.B.3, physical dependence is a real and absolute risk to *all* patients on chronic opioid therapy, and more severely so to those who were or are on moderate to high dose daily opioids. All patients who take opioids for longer than several days to several weeks will become physically dependent on opioids, even if taken exactly as prescribed and will suffer the real and serious consequences of withdrawal which may make them unable to stop. *See supra* Section IV.B.

j. Message 11: addiction is less than 1% or low or rare.

181. As set forth throughout this entire report, this is false. *See e.g. supra* Sections IV.E and IV.C.

182. Not only was the addiction rate or the implication that addiction itself was rare utterly false, but this message is designed to direct attention away from the nearly universal population of people who will become dependent on opioid after taking long-term opioids and the dangers and risks of having a population who cannot stop taking opioids. (*See supra* Section IV.B.) Moreover, as full described in this report, both science and history have shown these types of statements to be utterly false. *See supra* Section IV.E. Obviously, as the current

epidemic of dependence, addiction and overdose shows, this kind of message, designed to imply that opioids were low risk, was utterly reprehensible and lead to widespread harm. In fact, because of the terrible human experiment the Defendants decided to unleash on America we now have current and very real proof of the falsity of this message.

k. Message 12: Patients can be easily tapered off opioids.

183. This is only true when patients take opioids at low doses and for short durations. Otherwise it is false. The opioids of the 1970s and 1980s, with doses of 5-10 mg or at most 15 - 20 mg of hydrocodone or oxycodone, are *relatively* easy to taper off *if* the duration of care has been short. The long-term prescribing of escalating doses of opioids Defendants advocated for starting in the 1990s, and continuing through today, does not permit easy tapering. *(See supra* Section IV.B.) These higher doses and longer durations combine to contribute to much higher degrees of tolerance and dependence, which presents much more clinically difficult challenges for ceasing patients' use of opioids.[109] Purdue's 2007 guilty plea was based in part on criminally misrepresenting the incidence of OxyContin withdrawal.[110]

[109] Kosten, *supra* note 31, at 13-20; NASEM, *Pain Management and the Opioid Epidemic, supra* note 62, at 191 ("ER/LA formulations are associated with increased risks of diagnosis of substance abuse disorder (SUD) and nonfatal and fatal opioid overdose."); *CDC Guideline for Prescribing Opioids for Chronic Pain (Factsheet), supra* note 61 ("When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long acting opioids. . . . When opioids are started, clinicians should use the lowest effective dosage.").

[110] Agreed Statement of Facts, *supra* note 79, at ¶¶ 28-38.

l. Message 13: dependence is not a significant concern – it is "only" physical and easily reversed.

184. This is inaccurate. Physical dependence involves real, longitudinal adaptations in brain and body chemistry that are *not* easily reversed.[111] The adaptations of the brain and brain-stem to long-term, daily exposure to opioids in the normal, non-abusing and non-addictive person, while still poorly understood today, are certainly not trivial. That is why tapering off of long-term potent daily opioids continues to be such major clinical challenge.[112]

185. Dependence on opioids is a very serious clinical concern. (*See supra* Section IV.B.) Tapering more than 5% or at most 10% of the dose per month typically precipitates withdrawal with attendant anxiety / insomnia / and severe exacerbation of the pain. This typically sabotages the taper and results in continued use with a feeling of hopelessness and helplessness on the part of the patient and prescriber. Some patients with "just" physical dependence need to be admitted to a detox unit for inpatient medical withdrawal from the opioids or even enrolled in an opioid treatment program and treated with buprenorphine or methadone. And for many of these patients, even when they do taper off of high dose opioids, their brain function continues to be affected by the opioid for a prolonged period (complex physical dependence).[113] To suggest that only the "addicted people" are those who were put at substantial risk is utterly false. Indeed, Defendants caused millions of people to become

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[111] J.W. Younger, et al., *Prescription Opioid Analgesics Rapidly Change The Human Brain*, 152 Pain 8, 1803-1810 (2011); Kouyanou, et al., *Medication Misuse, Abuse And Dependence In Chronic Pain Patients*. 43 J. of Psychosomatic Research 5, 497-504 (1997).

[112] Jane C. Ballantyne & Cathy Stannard, *New Addiction Criteria: Diagnostic Challenges Persist In Treating Pain With Opioids*, 21 *Pain* 1-7 (2013).

[113] *Id.*

dependent on drugs that they were often powerless to quit. To suggest that dependence is inconsequential, normal or unharmful is untrue and allowed the widespread nature of the crisis we are in today.

m. Message 14: Drug abusers and potential addicts can be easily identified and therefore not prescribed opioids, or prescribed opioids and monitored closely.

186. A discussed *supra* Sections IV.D and IV.B.3.c. it is not easy for most physicians and advanced practitioners to identify people with abuse and addiction, and even more difficult for these physicians to identify *potential* addicts. The CDC Guideline for Prescribing Opioids for Chronic Pain found in its review of available evidence that available risk screening tools "show insufficient accuracy for classification of patients as at low or high risk for abuse or misuse."[114] Further, that a potential harm exists when insensitive screening tools underestimate a patient's risk, i.e., a false negative.[115]

187. It was therefore inaccurate for Defendants to promote the concept that opioids could continue to be prescribed liberally, because it is easy to identify "abusers" and potential "addicts" and simply avoid prescribing to those people.

n. Message 15: Even patients at high risk of addiction can be safely prescribed opioids by using risk-mitigation strategies such as pain contracts

188. Furthermore, even if high risk patients could be stratified, it would be false to instruct prescribers that they could manage patients' drug taking to prevent aberrant behaviors through interventions such as pain contracts. Implying that a typical prescriber can safely prescribe opioids on a chronic basis if they simply have a patient sign a contract regarding the

[114] CDC Guideline, *supra* note 1.

[115] *Id*. at 14.

risks and more carefully monitor the patient is analogous to encouraging them to provide "carefully monitored gin" to an alcoholic. This is clinically reckless and endangers the health and safety of the patient and the patients' family, as well as the safety of the community. Per the CDC, "[n]o study evaluated the effectiveness of risk mitigation strategies,"[116] and the risks of using these interventions unsuccessfully include higher risks of death.[117]

o. Message 16: Chronic Pain should be treated with opioids as a first resort; Message 17- All Pain Should be Treated With Opioids; Message 18- Undertreated Pain Should be Treated with Opioids

189. As discussed above in *supra* Section IV.C there is no good evidence that long-term opioids effectively treat chronic pain and there is substantial evidence that opioids prescribed long-term or to treat chronic pain puts patients at a significant risk of dependence, withdrawal, addiction, misuse, overdose and death. There was no science therefore to support that chronic conditions should be treated with opioids long-term and statements made in marketing to this effect were unfounded.

190. There is no real objective standard or bright line test delineating when opioids are appropriately given for long-term use or to treat chronic conditions. At most, opioids are properly indicated for the short-term treatment of moderate to severe acute pain (e.g. trauma or post-surgical pain); end-of-life pain/hospice care; and cancer pain from active malignant disease. Chronic opioid therapy is not recommended for most common chronic pain conditions (defined as moderate to severe pain lasting beyond 90 days), including low back pain, centralized pain such as fibromyalgia, and headache pain. In less common moderate to severe chronic pain

[116] *Id*. at 11.

[117] *See* Russell Portenoy Dep. Tr. 218:6-18, Jan. 24, 2019 (opioid-addicted patients more likely to die from respiratory depression if in active addiction and given higher doses of opioids).

conditions (such as pain from advanced multiple sclerosis, sickle cell disease, pain following spinal cord injury and paraplegia, or post-herpetic neuralgia), which comprise a small percentage of chronic pain patients, opioids may be considered a third-line therapy (taken if other therapies are ineffective or contraindicated).

191. Given the above narrow criteria for indicated chronic pain use and its role as third-line therapy, and the significant risks associated with its use, chronic opioid therapy for persons with chronic pain conditions is, at most, indicated in less than 10% of patients with chronic pain and likely significantly fewer. Among all opioids prescribed for long-term use (i.e. prescriptions written for 90 days, or 30 days with refills, including for acute conditions, this percentage is much smaller. For all proper indications other than hospice care, if prescribed, opioids should be prescribed with the lowest effective dose of preferably immediate-release opioids, taken only when needed and only as long as necessary.

192. Marketing that did not provide these important and very restrictive limitations was dangerous, lacked scientific basis and was designed to mislead prescribers into thinking opioids could be far more widely prescribed than is safe or was proven effective. This kind of expansive and unlimited marketing clearly contributed to the massive amount of pills that were prescribed across a wide swatch of patients for a wide swath of conditions directly leading to the epidemic we have in America today.

193. As discussed in *supra* Section IV.H.2, marketing that implied or stated that Defendants had developed a new, different or safer solution to undertreated pain was simply false. Defendants' drugs were no different and no less risky than opioids that existed before they came on the market and in fact, because of their potency and their marketing for long-term use at any duration and dose were far more dangerous.

p. Messages 19: There is more risk of leaving pain untreated than using opioids to treat pain.

194. This is a myth, the advocation of which has resulted in a shortening of the national life expectancy for the first time in 50 years.[118] The American public had chronic pain treated by non-opioid therapy for decades, and accidental fatal overdose on prescription opioids was rare. Then the myth that chronic pain, if not treated with opioids, was somehow a major clinical risk was promulgated and widely disseminated. This triggered the subsequent massive rise in opioid prescribing and increased exposure that resulted in accidental fatal overdose on prescription drugs becoming the number one reason for accidental death in the entire nation and, resulted in a wide population dependent on and addicted to opioids [119] In short, the risk of addiction, dependence overdose and death never should have been trivialized, left out or deemphasized in the conversation about pain and no one ever should have promoted the concept that leaving pain untreated was akin to malpractice absent a less risky solution than opioids.

q. Message 20: Opioids offer more effective and safer pain control than alternative treatments for pain

195. The "safety" of opioids was over-emphasized, and mischaracterized, the risks of non-opioid medications was over-emphasized, and the costs and logistical challenges of non-pharmacologic treatment of pain was emphasized – all of this strongly encouraged and inappropriately encouraged more prescribing of opioids than ever should have been prescribed and exposing a wide population of people to dangerous and addictive drugs. *See generally supra* Section IV.D.

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[118] Jiaquan Xu, et al., *Mortality in the United States, 2015*, Nat'l Ctr. for Health Stats., NCHS data brief, no 267 (2016), https://www.cdc.gov/nchs/products/databriefs/db267.htm.

[119] *Id*; Jiaquan Xu, et al., *Deaths: Final Data for 2016*, 67 Nat'l Vital Stats. Report 5, (July 26, 2018), https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_05.pdf.

196. In particular, claims that opioids were safer or more effective than NSAIDs (such as anti-inflammatories) were false. (*See supra* Section IV.E.) Data shows that opioids have a greater risk of adverse events – including risk of cardiovascular events, respiratory depression, fractures and injury – than NSAIDs.[120]

197. Defendants also contrasted their opioids with NSAIDs by emphasizing that their drugs did not have a "ceiling dose," in contrast with NSAIDs. In reality, and as the CDC Found, the risks of high dose opioids (greater than or equal to 90 mg morphine milligram equivalents per day), while "risks for serious harms related to opioid therapy increase at higher opioid dosage[,] including "motor vehicle injury, opioid use disorder, and overdose[.]"[121]

198. To suggest that opioids were safer than treatment like NSAIDS (anti-inflammatories) is simply untrue and put numerous patients at risk.

r. Message 21: Defendants' opioids will make your life better without risk

199. As discussed in *supra* Section IV.C, opioids have not been proven to improve chronic pain patients' function or quality of life. Therefore, Defendants' marketing showing highly functional pain patients, or claims of improving quality of life, were misleading and failed to highlight the real and serious risks of these drugs, as discussed throughout this paper. *(See e.g. supra* Section IV.E.)

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[120] Daniel Solomon, et al., *The Comparative Safety of Analgesics in Older Adults with Arthritis*, 170 Arch. Intern. Med. 22, 1968-76 (2010); Lydia Rolita, et al., *Greater Number of Narcotic Analgesic Prescriptions for Osteoarthritis is Associated with Falls and Fractures in Elderly Adults*, 61 J. Am. Geriatric Soc., 335-40 (2013); L.E. Chaparro, et al., *Opioids Compared to Placebo or Other Treatments for Chronic Low-Back Pain*, 8 Cochrane Database Systems Rev., CD004959.

[121] CDC Guideline, *supra* note 1, at 22-23.

200. As discussed above in *supra* Section IV.B, at best, there was some evidence of short-term comfort as a result of opioids.[122] However, most studies involving long-term opioid use showed worsening pain, function and quality of life.[123] Yet despite the data, the defendants misleadingly over emphasized improvements in function and comfort, while not being truthful about the risks associated with opioid use. Defendants were repeatedly warned by the FDA that certain of their advertisements improperly suggested Opioids would lead to functional improvement gains.[124]

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[122] Kathryn P. Anastassopoulos, et al., *Reported Side Effects, Bother, Satisfaction, And Adherence In Patients Taking Hydrocodone For Non-Cancer Pain*, 9 J. Opioid Mgmt. 2, 97-109 (2013), doi: 10.5055/jom.2012.0151; Roger Chou, et al., *The Effectiveness And Risks Of Long-Term Opioid Treatment Of Chronic Pain,* Agency for Healthcare Research and Quality (Sept. 2014), http://www.effectivehealthcare.ahrq.gov/ehc/products/557/1971/chronic-pain-opioid-treatment-report-141007.pdf.

[123] J. Eriksen, et al., *Critical Issues On Opioids In Chronic Non-Cancer Pain: An Epidemiological Study*, 125 Pain, 172-9 (2006);

P. Sjogren, et al., *A Population-Based Cohort Study On Chronic Pain: The Role Of Opioids*, 26 Clinical J. Pain, 9, 763-9 (2010); K.S. Dillie, et al., *Quality Of Life Associated With Daily Opioid Therapy In A Primary Care Chronic Pain Sample*, 21 J. Am. Board Family Medicine 2, 108-117 (2008); Gary Franklin, et al., *Early Opioid Prescription And Subsequent Disability Among Workers With Back Injuries: The Disability Risk Identification Study Cohort*. 33 Spine 2, 199-204 (2008); Gary M. Franklin, et al., *Opioid Dosing Trends And Mortality In Washington State Workers' Compensation, 1996-2002*, 48 Am. J. Indus. Medicine, 2, 91-9 (2005); J.A. White, et al., *The Effect Of Opioid Use On Workers' Compensation Claim Cost In The State Of Michigan*, 54 J. Occup. Enviro. Medicine 8, 948-53 (2012); Gary Franklin, et al., *Opioid Use For Chronic Low Back Pain: A Prospective, Population-Based Study Among Injured Workers In Washington State, 2002-2005*, 25 Clinical J. Pain 9, 743-51 (2009).

[124] *See* PKY181392830, Jan. 17, 2003 Letter to Purdue, at 5; ACTAVIS0006307, Feb. 18, 2010 Letter to Actavis, at 3.

s. Message 22: There is no maximum or ceiling dose (i.e., "titrate to effect" concept from cancer/palliative care should be used with chronic pain).

201. The clinical fact that the brain has an unlimited ability to develop tolerance to opioids, if taken as directed and slowly titrated over time, especially in palliative care, was characterized to convey that the prescriber and patient do not need to worry about tolerance and escalating doses of opioids in the chronic pain setting. This was false. *(See supra* Section IV.B.3.) Indeed, studies show that the higher the dose of opioids, the higher the risk of adverse events, including addiction, overdose and death.[125] In fact, many guidelines, including the 2016 CDC guidelines, recommend avoiding doses of over 50-100 MME.[126]

t. Message 23: Opioids can be prescribed for any pain condition without risk

202. As this entire report has emphasized, this is false. Opioids cannot be prescribed without risk to patients. Opioids are risky and dangerous. (*See supra* Section IV.B.) Indeed, it is because opioid prescribing is risky that guidelines, such as the 2007 Washington State and 2016 CDC opioid prescribing guidelines, were issued to contradict this type of false message. Further, as more fully explained in *supra* Section IV.C, long-term opioids never should have been prescribed widely for all types of pain conditions and are inappropriately prescribed for conditions like back pain, fibromyalgia and headache, especially at high doses and for long durations.

[125] NASEM, *Pain Management and the Opioid Epidemic*, *supra* note 62, at 193.

[126] CDC Guideline, *supra* note 1 ("Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥ 50 morphine milligram equivalents (MME)/day.").

u. Message 24: Opioids can be prescribed to any age group without risk

203. This is not true. Opioids in pregnancy produce neonatal abstinence. Exposure to opioids in adolescence increases the risk of abuse of opioids in college. One of the "poor prognostic signs" regarding increased risk of opioid abuse was prescribing for chronic pain complaints in young adults. The FDA has also recognized the heightened risk to older patients of treatment with opioids.[127]

v. Message 25: "Round the clock" dosing should be used for chronic pain rather than "as needed" dosing

204. This is not always true. Round the clock dosing may be useful in some patients who need opioids for chronic pain that is fairly constant in character, but that is a very small proportion of patients with chronic pain. *See supra* Section IV.C. Prescribing opioids daily round the clock (see ER/LA comments above) increases exposure, reinforces a habit of taking opioids on a schedule and not as needed to control pain, and maximizes the chance of physical dependence and withdrawal. *See supra* Section IV.B.3.c. It was for this reason the FDA ordered changes in 2014 to the indications of ER/LA opioids for "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and *for which alternative treatment options are inadequate*."[128] The CDC Guideline also noted that ER/LA opioids carry "serious

[127] *Opioid Use In The Older Adult Population*, SAMSHA (Aug. 15, 2017), https://www.samhsa.gov/capt/sites/default/files/resources/resources-opiod-use-older-adult-pop.pdf; Jane Tilly, et al., *The Opioid Public Health Emergency and Older Adults*, Admin. for Community Living (Dec. 12, 2017), http://www.nasuad.org/node/70191.

[128] PURCHI-000483401 (April 16, 2014 OxyContin label) (emphasis added).

risk" and are associated with "substantially higher dosages,"[129] and recommended prescribers initiate opioid therapy, if at all, with immediate release opioids on an as-needed basis.

w. Message 26: "Breakthrough pain" applies to chronic pain, not just cancer pain, and short-acting opioids should be used to supplement long-acting opioids to treat breakthrough pain.

205. Break-through pain ("BTP") is an acute pain and malignant pain concept. It has little if any applicability to chronic pain conditions. Foisting this concept of taking extra short acting opioids for BTP on top of longer acting opioids in chronic pain drives up tolerance, drives up doses, drives up physical dependence, drives up potential withdrawal intensity, and has no good research supporting the practice. It is a sales bonanza at the expense of increased patient tolerance, physical dependence and risk of addiction. *See supra* Sections IV.E and IV.B.3. It also is a message that is used to distract from the fact that Q12 dosing often does not provide a consistent 12 hours of pain relief.[130]

206. All of these false, inaccurate or misleading themes and messages appear designed to create the impression that the Defendants' Drugs were less risky than opioids of the past and to influence the type of massive change in prescribing that occurred starting in the 1990s and continuing to present.

I. Literature Used by Defendants to Promote Opioids

207. I was asked to review certain documents used by Defendants in marketing, sales training and internal documents and the messages that were contained in these publications (I

[129] CDC Guideline, *supra* note 1, at 13, 21.

[130] Pain relief not lasting for 12 hours is a particular concern for OxyContin, and the fact it did not provide 12 hours of pain relief to most patients was known to Purdue in its clinical program. *See* FDA Medical Officer Review, PKY180698976 ("Patients used about 1-2 doses of rescue a day and found it an important part of therapy").

understand these documents will be identified in Schedule 14 to the Expert Report of Matthew Perri, BS Pharma, PhD, RP). I have been asked to assess the messages contained in those publications and offer opinions regarding the propriety or impropriety of Defendants using those publications to promote the large-scale use of opioids to treat chronic pain or for long-term use. My opinions are as follows.

1. Porter and Jick

208. One of the pieces cited by Defendants in marketing (*See* Perri Schedule 14) was a Letter to the Editor "Addiction rare in patients treated with narcotics," that Jane Porter and Hershel Jick wrote about a hospitalized population in 1980.[131] This letter does not support the concept that the risk of addiction for prescription opioids was "rare" or low, or that opioids should have been used widely to treat chronic pain or for long-term use.[132] This eleven-line letter to the editor has no details, applies only to a hospitalized patient population, and has no information what-so-ever about whether these patients had acute, chronic or malignant pain.[133] Referencing this as data regarding the risks of long-term opioid use, or as supporting the use of opioids in chronic pain management, is deceptive and lacks any shred of scientific or clinical validity.

209. Despite this, as Perri Report Schedule 14 shows, the Porter and Jick letter was cited by Defendants as if it was a credible scientific study on such issues.

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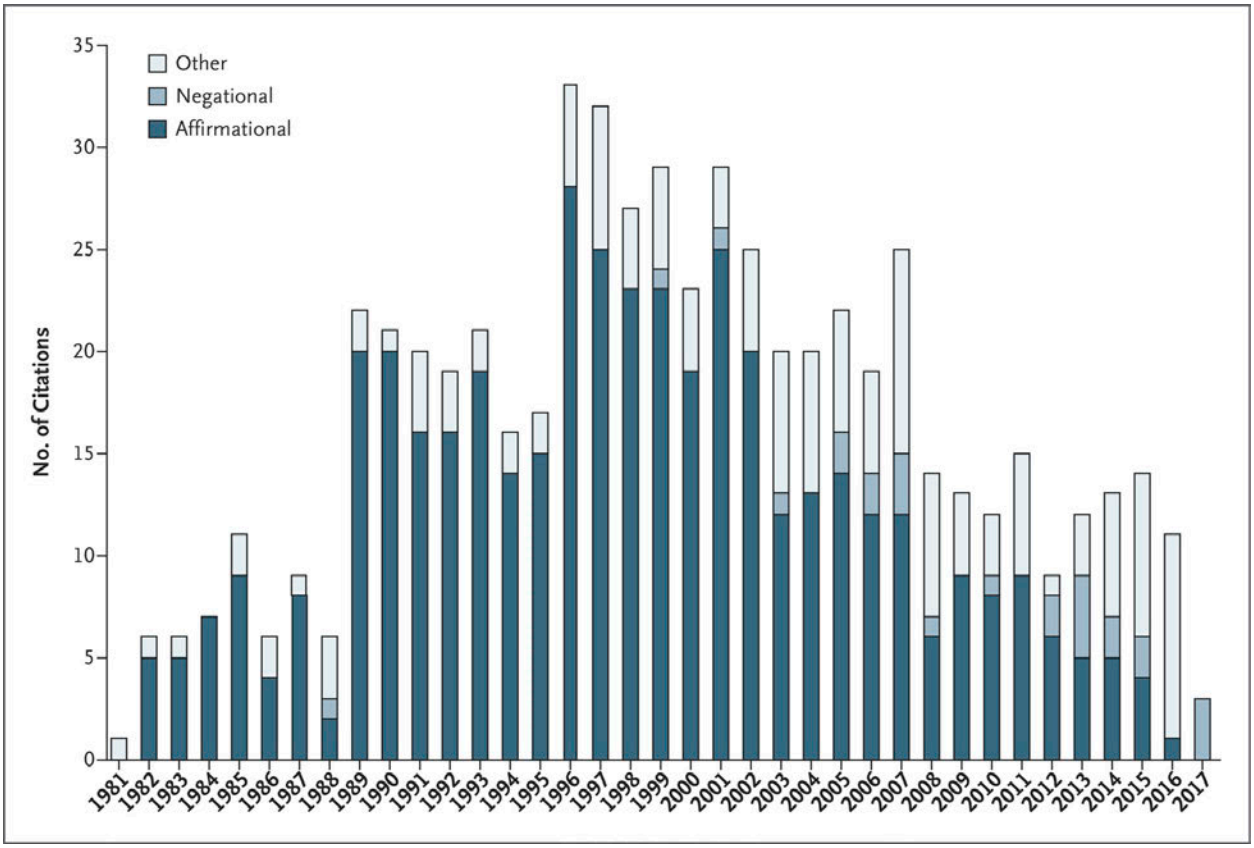
[131] Jane Porter & Hershel Jick, *Addiction Rare In Patients Treated With Narcotics*, The New Eng. J. of Medicine at 123 (1980).

[132] *Id*.

[133] *Id*.

210. The pharmaceutical industry's widespread misuse of this letter was studied and the results published in a letter to the New England Journal of Medicine by Dr. David Juurlink, at the University of Toronto, and coauthors Pamela T.M. Leung, Erin M. Macdonald, and Matthew B. Stanbrook, M.D., Ph.D, Irfan A. Dhalla, M.D. Dr. Juurlink's review "identified 608 citations of the index publication and noted a sizable increase after the introduction of OxyContin (a long-acting formulation of oxycodone) in 1995 (Figure 1):"[134]



Dr. Juurlink's review reports that "[o]f the articles that included a reference to the 1980 letter, the authors of 439 (72.2%) cited [Porter and Jick] as evidence that addiction was rare in patients

[134] Pamela T.M. Leung, et al., *A 1980 Letter on the Risk of Opioid Addiction (Correspondence)*, The New Eng. J. of Medicine (June 1, 2017), https://www.nejm.org/doi/full/10.1056/NEJMc1700150.

treated with opioids."[135] Additionally, "[o]f the 608 articles, the authors of 491 articles (80.8%) did not note that the patients who were described in the letter were hospitalized at the time they received the prescription, whereas *some authors grossly misrepresented the conclusions of the letter*."[136] Dr. Juurlink and his colleagues concluded:[137]

> In conclusion, we found that a five-sentence letter published in the Journal in 1980 was heavily and uncritically cited as evidence that addiction was rare with long-term opioid therapy. We believe that this citation pattern contributed to the North American opioid crisis by helping to shape a narrative that allayed prescribers' concerns about the risk of addiction associated with long-term opioid therapy. In 2007, the manufacturer of OxyContin and three senior executives pleaded guilty to federal criminal charges that they misled regulators, doctors, and patients about the risk of addiction associated with the drug.

211. The impropriety of the pharmaceutical industry's use of this letter to market opioids was subsequently made clear by the author himself, Hershel Jick. Dr. Jick has stated that he never meant the letter to the editor to be used for support that opioids are safe and effective for long-term use and to treat chronic pain.[138] Dr. Jick stated "[o]nly years and years later, that letter was used to advertise by new companies that were pushing out new pain drugs… I was sort of amazed. None of the companies came to me to talk to me about the letter, or the use as an ad."[139] Dr. Jick went on to say that the drug companies used his letter to state that their new

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[135] *Id.*

[136] *Id.* (emphasis added).

[137] *Id.*

[138] Taylor Haney & Andrea Hsu, *Doctor Who Wrote 1980 Letter On Painkillers Regrets That It Fed The Opioid Crisis*, NPR (June 16, 2017), https://www.npr.org/sections/health-shots/2017/06/16/533060031/doctor-who-wrote-1980-letter-on-painkillers-regrets-that-it-fed-the-opioid-crisi.

[139] *Id.*

opioids were not addictive even though "*that's not in any shape or form what we suggested in our letter*."[140] Dr. Jick concluded by stating that he regrets the letter because of the way it was misused, stating "[t]he letter wasn't of value to health and medicine in and of itself. So if I could take it back — if I knew then what I know now, I would never have published it. It wasn't worth it."[141]

212. Indeed, Dr. Jick contacted Purdue in 2003, noting that the NEJM publication was "only a letter" and suggesting a study from much broader data available to him to more fully assess the risk of addiction from opioid use.[142]

213. Defendants' use of this letter to promote the concept that the risk of addiction to Defendants' Drugs was rare was improper and simply reprehensible.

2. Portenoy and Foley

214. Similar to Porter and Jick, it was inappropriate and misleading for Defendants to use Russell Portenoy and Kathleen Foley's 1985 paper, "Chronic use of opioid analgesics in non-malignant pain: report of 38 cases," [143] to widely promote opioids by claiming they were "rarely addictive."

215. As seen in Schedule 14 to the Perri Report, the Portenoy and Foley paper was used by the Defendants in marketing.

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[140] *Id* (emphasis added).

[141] *Id.*

[142] PPLPC052000001210.

[143] Russell K. Portenoy & Kathleen M. Foley, *Chronic Use Of Opioid Analgesics In Non-Malignant Pain: Report Of 38 Cases*, Pain 25.2, 171-186 (1986).

216. Using this paper to promote long-term and wide-spread use of opioids to treat chronic pain was simply inappropriate. Citing the paper as evidence that addiction was rare in patients who are receiving long-term opioids is both improper and misleading.

217. The Portenoy and Foley paper is the weakest of scientific study design – a case series. A case series regarding 38 patients is not a credible scientific research method to support any large-scale clinical recommendations. It is certainly an insufficient basis to recommend the use of opioids to treat chronic pain or to suggest that the risks of doing so are slight. Problems with case series include selection bias (selecting a biased group of patients in the first place), recall bias (perhaps not recalling all patients who were treated this way and thus leaving patients out of the series), retrospective design (looking backwards at patients in hind-sight tends to lead to incomplete data and monitoring for outcome objectives), lack of any control group, lack of randomization between treatments, as well as many additional scientific flaws. This is why case series should not be used to recommend anything but potential future areas for further clinical research with a stronger methodological design. It is clinically irresponsible to suggest anything else based on one or more case series, especially one involving 38 patients.

218. Portenoy and Foley's conclusion from a case study of 38 patients that "opioid maintenance therapy can be a safe, salutary and more humane alternative to the options of surgery or no treatment in those patients with intractable non-malignant pain and no history of drug abuse" is inconsistent with accepted standards of scientific research and clinical decision making. The use of this article to support widely marketing Defendants' Drugs to treat long-term chronic pain was simply misleading and inappropriate.

219. Russell Portenoy agrees. In an interview with the Wall Street Journal, Dr. Portenoy stated, "[d]id I teach about pain management, specifically about opioid therapy, in a

way that reflects misinformation? Well, against the standards of 2012, I guess I did. We didn't know then what we know now."[144] Additionally, the article reports how in an earlier interview Dr. Portenoy stated that he "gave innumerable lectures in the late 1980s and '90s about addiction that weren't true," and it was "quite scary" to think how the growth in opioid prescribing was driven by people like him and had contributed to soaring rates of addiction and overdose deaths.[145] Dr. Portenoy was quoted as saying, "[c]learly, if I had an inkling of what I know now then, I wouldn't have spoken in the way that I spoke. It was clearly the wrong thing to do."[146]

220. However, there never was any scientific basis for using Dr. Portenoy's article as a basis for promoting long-term opioid use. The science and understanding of the risks of opioids, particularly if taken long-term and at high doses, was known throughout this period and it underwent no fundamental change in 2012 or after.

221. As Schedule 18 from the Perri Report shows, and the Wall Street Journal research indicates, Dr. Portenoy and his institution took millions of dollars from Defendants including Purdue, Endo, Allergan, and Johnson and Johnson.[147] Likewise, Kathleen Foley has testified that she was funded by the pharmaceutical industry at the time she and Dr. Portenoy wrote this publication.[148]

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[144] Thomas Catan & Evan Perez, *A Pain-Drug Champion Has Second Thoughts*, Wall Street J. (Dec. 17, 2012), https://www.wsj.com/articles/SB10001424127887324478304578173342657044604.

[145] *Id.*

[146] *Id.*

[147] *Id; see also* Schedules 17 and 18 to Perri Report.

[148] Kathleen Foley Dep. Tr. at 7-8, August 2004.

3. APS/AAPM Consensus Statement

222. Defendants also used the 1997 publication, "The Use of Opioids for the Treatment of Chronic Pain: A consensus statement from the American Academy of Pain Medicine and the American Pain Society," to market opioids. *See* Perri Schedule 14.

223. This Consensus Statement, authored in 1997 by two pain specialty professional societies that have taken money from Defendants,[149] contains a number of messages that are inaccurate or false. Indeed, the Consensus Statement emphasizes the negatives of failing to treat pain while trivializing the real and serious risks of addiction and death associated with opioids.[150] For example, the Statement states, "[p]ain is one of the most common reasons people consult a physician, yet it frequently is inadequately treated, leading to enormous social cost in the form of lost productivity, needless suffering, and excessive healthcare expenditures" while identifying "impediments to the use of opioids" as being "concerns about addiction, respiratory depression and other side effects, tolerance, diversion, and fear of regulatory action."[151]

224. The Consensus Statement makes the statement that "[c]urrent information and experience suggest that many commonly held assumptions need modification" and then goes on to address what it calls "misconceptions." None these are actually misconceptions, however, and suggesting so is irresponsible and wrong. I will address the so-called "misconceptions" in turn.

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[149] *See* Schedules 17 and 18 to the Perri Report.

[150] AAPM & APS, *The Use of Opioids for the Treatment of Chronic Pain: A consensus statement from the American Academy of Pain Medicine and the American Pain Society*, 6 J. of Pain 1, 77-79 (1997)

[151] *Id.*

225. The Consensus Statement first states that practitioners may have a "misconception" regarding the addictiveness of opioids when used for chronic pain, stating that:

> **Addiction.** Misunderstanding of addiction and mislabeling of patients as addicts result in unnecessary withholding of opioid medications. Addiction is a compulsive disorder in which an individual becomes preoccupied with obtaining and using a substance, the continued use of which results in a decreased quality of life. Studies indicate that the de novo development of addiction when opioids are used for the relief of pain is low. Furthermore, experience has shown that known addicts can benefit from the carefully supervised, judicious use of opioids for the treatment of pain due to cancer, surgery, or recurrent painful illnesses such as sickle cell disease.

226. The false or inaccurate statements in this statement are numerous (many of which have been thoroughly addressed in *supra* Sections IV.B and IV.B.3.

227. This Consensus Statement contains many of the myths about low risk for addictive disease and the ability to provide opioids to those with addictive disease that fueled excessive prescribing and the mounting national opioid death rate.

228. The Consensus Statement also states that practitioners may have a "misconception" regarding the seriousness of respiratory depression risks associated with opioids, that "it is now accepted by practitioners" that "respiratory depression induced by opioids tends to be a short lived phenomenon," and that withholding opioids based on concerns about respiratory depression is "unwarranted," stating in full:

> **Respiratory depression and other side effects:** Fear of inducing respiratory depression is often cited as a factor that limits the use of opioids in pain management. It is now accepted by practitioners of the specialty of pain medicine that respiratory depression induced by opioids tends to be a short-lived phenomenon, generally occurs only in the opioid-naive patient, and is antagonized by pain. Therefore, withholding the appropriate use of opioids from a patient who is experiencing pain on the basis of respiratory concerns is unwarranted. Other side effects, such as constipation, can usually be managed by attention to diet, along with the regular use of stool softeners and laxatives. Sedation and nausea, possible early side effects, usually dissipate with continued use.

229. There are many false or inaccurate statements in this excerpt and the message that respiratory depression is not a serious concern or may be a "unwarranted" basis to withhold opioids is perhaps the worst. In fact, respiratory depression is the primary cause of accidental fatal opioid overdoses. Thousands die annually of respiratory depression and to minimize its seriousness is simply reprehensible.

230. Another "misconception" identified in the Consensus Statement contains numerous false and very dangerous statements, including:

> **Tolerance:** It was previously thought that the development of analgesic tolerance limited the ability to use opioids efficaciously on a long-term basis for pain management. Tolerance, or decreasing pain relief with the same dosage over time, has not proven to be a prevalent limitation to long-term opioid use. Experience with treating cancer pain has shown that what initially appears to be tolerance is usually progression of the disease. Furthermore, for most opioids, there does not appear to be an arbitrary upper dosage limit, as was previously thought.

231. These types of statements are false and misleading. *See* in *supra* Section IV.B.3.a. They directly lead to the epidemic we see today. As discussed previously, it is false that no dose of opioid is too high to be risky and exposing patients to high doses of these dangerous narcotics most certainly contributed to addiction, overdose and death. Further, it is utterly false to suggest that need for higher doses is often the result an escalation of disease or pain rather than tolerance. Additionally, the appropriate response to an escalation of disease is reevaluation of the patient and additional interventions, not necessarily an increase in opioids.

232. Finally, the Consensus Statement states that concerns about diversion should not be a limitation on opioid prescribing. The Statement says:

> **Diversion:** Diversion of controlled substances should be a concern of every health professional, but efforts to stop diversion should not interfere with prescribing opioids for pain management. Attention to patterns of prescription requests and the prescribing of opioids as part of an ongoing relationship between a patient and a healthcare provider can decrease the risk of diversion.

233. This is utterly false and very dangerous. Indeed, the point of this statement appears to be to reduce prescriber concerns about diversion and minimize that factor in physician decision making when deciding whether to prescribe opioids. Diversion endangers the health and safety of the community, since it results in exposure of others – often without pre-existing tolerance – to high potency opioid pharmaceuticals that can be fatal on the first episode of use.

4. FSMB Model Guidelines

234. As cited in Schedule 14 to the Perri Report, Defendants also used the Federation of Medical Boards of the United States, Inc. "Model Guidelines for the Use of Controlled Substances for the Treatment of Pain." May 2, 1998 (FSMB Model Guidelines) in marketing. Purdue Pharma alone distributed 300,000 copies of the FSMB Model Guidelines through its sales force to physicians just between 1999 and 2002.[152]

235. The FSMB Model Guidelines were authored by various pain organizations, including the same organizations that wrote the Consensus Statement, namely the American Pain Society and the American Academy of Pain Medicine, as well as the Wisconsin Pain and Policy Study Group.[153] As reflected by Schedule 18 to the Perri Report, each were funded by Defendants.

236. The FSMB Guidelines imply a right to treatment of pain and improperly emphasize treatment of pain while failing to mention or trivializing addiction, stating that "inadequate pain control may result from physicians' knowledge about pain management or an inadequate understanding of addiction" and that "fear of investigation" may result in "inadequate

[152] PDD1716030173.

[153] Federation of Medical Boards of the United States, Inc., *Model Guidelines for the Use of Controlled Substances for the Treatment of Pain* (May 2, 1998) (hereinafter "FMB, *Model Guidelines*").

treatment of chronic pain patients."[154] Additionally, the FSMB Model Guidelines downplay concerns about dependence and state that "opioid analgesics, may be essential" in the treatment of pain.[155]

237. The Guidelines also paved the way to more liberal use of opioids by telling doctors that they "should not fear disciplinary action from the Board or other state regulatory or enforcement agency from prescribing, or administering controlled substances, including opioid analgesics, for a legitimate medical purpose," and that state licensing authorities "will not take disciplinary action against a physician for strictly adhering to these guidelines."[156]

238. Thus, by re-assuring physicians that they were unlikely to suffer medical board action for prescribing opioids, the FSMB Model Guidelines were designed to make doctors more comfortable in prescribing opioids.

239. Medical board guidelines are aimed at ultimately influencing medical practice and, indeed, doctors fear medical board action against their licenses. I have taught thousands of practitioners who have experienced medical board investigations of their prescribing practices. Concern about medical board review had historically been one of the factors that has helped control the prescribing of controlled drugs, and referring to medical board supervision had been a tool to assist physicians in explaining to patients why they cannot prescribe everything that is requested when it comes to controlled drugs. As medical boards were enlisted in this effort to reassure prescribers about the reasonableness of long-term opioids for chronic pain, this proved

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[154] *Id.*

[155] *Id.* at Section I: Preamble.

[156] *Id.*

to be a strong factor in increasing prescribing. Loss of concern regarding over-sight, and "permission" to longitudinally prescribe were influential in the change in prescribers' clinical behavior.

5. JCAHO Pain Standards

240. Physicians also practice in hospitals. And physician and nursing behavior can be influenced by hospital standards. One of the most influential drivers of behavior in hospital systems are standards issued by the Joint Commission on the Accreditation of Healthcare Organizations. Because accreditation is often necessary to doing business – it can play a role in everything from obtaining insurance to participation in group plans or receiving state or federal reimbursement – JCAHO has enormous influence over hospitals and thus the healthcare providers who work in hospitals. Hospitals are *very* concerned about their JCAHO Certification

241. As cited by in Schedule 14 to the Perri Report, Defendants cited to and used in marketing JCAHO's "Joint Commission on Accreditation of Healthcare Organizations Pain Standards for 2001" (2001).[157]

242. The JCAHO standards stated that patients had a "right" to treatment of pain and set standards that treatment must be assessed and treated.[158] The pain standards required that all patients admitted into the hospital be asked whether they had pain, no matter what the presenting condition.[159] Hospitals were then assessed on how well they treated their patients' pain.[160] The Standards say that pain is a "fifth" vital sign.[161]

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[157] Joint Commission on Accreditation of Healthcare Organizations, *Pain Standards for 2001* (2001).

[158] *Id.* at RI-14.

[159] *Id.*

243. Treating pain is a legitimate goal. But treating pain as a "fifth vital sign" as if it were a life or death issue (like other vital signs) and assessing all patients for pain, no matter what their presentation is, or making hospital certification scores depend on patient ratings of how well their pain was treated, was a tremendous mistake, and drove a systematic intervention to identify and then treat all pain complaints in pharmacologically aggressive ways. It influenced physician and healthcare provider behavior and inappropriately drove opioid prescribing.

244. In fact, in studying the application of the JCAHO pain standards, a 2007 study observed that "[t]he perceived authority of the JCAHO mandate creates great psychological pressure on caregivers" and that the "emphasis on undermanagement of pain is heightened by JCAHO guidelines that all patients with a VAS [Visual Analogue Scale for pain] of five or greater must be assessed. This assessment in many busy PACUs [Post Anesthesia Care Units] and even SICUs [Surgical Intensive Care Units] often leads to additional administration of opioids."[162]

245. In recognition of these shortcomings, in June 2016, delegates at the annual meeting of the American Medical Association voted for a resolution to remove Pain as the Fifth Vital Sign.[163]

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[160] *Id.*

[161] *Id.*

[162] Charles E. Lucas, et al., *Kindness Kills: The Negative Impact of Pain as the Fifth Vital Sign*, 205 J. Am. Coll. Surg., no. 1, 2007, at 105, doi:10.1016/j.jamcollsurg.2007.01.062.

[163] Steven R. Johnson, *AMA Seeks Move Toward Opioid Alternatives*, Modern Healthcare (June 15, 2016), https://www.modernhealthcare.com/article/20160615/NEWS/160619941/ama-seeks-move-toward-opioid-alternatives.

6. American Geriatric Society Panel on Persistent Pain in Older Persons- 2002

246. As cited in Schedule 14 of the Perri Report, Defendants also marketed using the American Geriatrics Society's Panel on Persistent Pain in Older Persons. The management of persistent pain in older persons, Journal of the American Geriatrics Society 50.6 Suppl (2002). As reflected by Table 18 to the Perri Report, the AGS was funded by at least several of the Defendants.

247. The AGS Guidelines contain messages similar to those examined above in other funded Defendant funded publications, including the following messages:

i. "Reluctance to prescribe these drugs has probably been over-influenced by political and social pressures to control illicit drug use. In fact, incidence of addictive behavior among patients taking opioid drugs for medical indications appears to be very low."

ii. "the chronic use of opioids for persistent pain or some other analgesic strategies may have fewer life-threatening risks than does the long-term daily use of high-dose non-selective COX NSAIDS."

iii. "The use of opioid analgesics for persistent noncancer pain is becoming more acceptable."

iv. "Physical dependence is an inevitable consequence of continuous exposure and is managed by gradual dose reduction (tapering) over the course of several days to weeks if indications for opioid therapy no longer exist;"

v. "True addiction (drug craving and continued use despite known harms) in older patients with persistent pain syndromes is probably rare in comparison with the known prevalence of undertreated debilitating pain"

vi. "Any change in a patient's drug requirements signals a need for reassessment for new or progressing disease before a diagnosis of 'opioid tolerance' is made;"

vii. "Concerns over drug dependency and addiction do not excuse the failure to relieve pain;"

248. The types of message included in this publication are designed to allay fears about the risks of opioids and do so inappropriately. For example, downplaying physical dependence and tolerance, and giving the impression that it is easy to remove patients from opioids, is inaccurate. *See supra* Section IV.B.3.a and IV.B.3.b.

249. Other statements, such as those stating that addiction is "rare," contained in the AGS Guidelines are simply false. *See supra* Section IV.E.

250. The statements downplaying dependence and discussing the alleged "ease" of tapering patients off opioids are false or at best misleading.

251. Other statements trivializing addiction and advocating prescribing in the face of concerns over dependency and addiction are simply irresponsible.

7. <u>FSMB Model Policy- 2004</u>

252. Defendants also cited another FSMB publication, the Model Policy for the Use of Controlled Substances for the Treatment of Pain (2004), in their marketing efforts.[164] See Perri Schedule 14. That publication also contained inaccurate statements that were improper to use to widely expand the market for prescription opioids for long-term use, including:

[164] FMB, *Model Policy for the Use of Controlled Substances for the Treatment of Pain* (May 2004), https://www.ihs.gov/painmanagement/includes/themes/newihstheme/display_objects/documents/modelpolicytreatmentpain.pdf.

i. That the "perception that prescribing adequate amounts of controlled substances will result in unnecessary scrutiny by regulatory authorities;"

ii. "Misunderstanding of addiction and dependence" contributes to "the prevalence of undertreated pain;"

253. The Model Policy then went on to establish a standard that doctors can be disciplined for failing to treat pain: "state medical boards will consider inappropriate treatment, including the undertreatment of pain, a departure from an acceptable standard of practice." In fact, the Model Policy was "revised to emphasize the professional and ethical responsibility of the physician to assess patients' pain."

254. As outlined above, these sorts of FSMB or local State medical board guidelines diminished the appropriate sense that long-term opioid prescribing was a potential danger to patients, to communities and to prescribers and created a new standard that "failing to treat pain" is akin to malpractice on the part of doctors. Of course, Defendants used this kind of "policy" in marketing to tell doctors that provided the solution to satisfy their duty to treat pain.

8. Fishman's Responsible Opioid Prescribing

255. Another publication widely distributed by Defendants was a book by Scott Fishman, M.D. entitled Responsible Opioid Prescribing: A Clinician's Guide (Waterford Life Sciences, 2007).[165] *See* Perri Report Schedule 14. As Schedule 18 to the Perri Report States, the book's author was a paid speaker for Defendants, and Defendants funded the FSMB, which published the book.

256. While the book's title sounds admirable, its contents contain inaccurate, false and misleading messages similar to the ones examined throughout this report, including:

[165] Scott Fishman, *Responsible Opioid Prescribing: A Clinician's Guide* (2007).

i. "Concurrent with the epidemic of prescription drug abuse" that there is an "equally legitimate cause of undertreated pain;"

ii. "Opioid therapy to relieve pain and improve function is a legitimate medical practice for acute and chronic pain of both cancer and non-cancer origin;"

iii. "Patients should not be denied opioid medications except in light of clear evidence that such medications are harmful to patient;"

iv. "Four key factors contribute to the ongoing problem of undertreated pain: (1) lack of knowledge of medical standards, current research and clinical guidelines for appropriate pain treatment (2) the perception that prescribing adequate amounts of opioids will result in unnecessary scrutiny by regulatory authorities (3) misunderstanding of addiction and dependence; and (4) lack of understanding of regulatory policies and processes."

v. "Be aware of the distinction between psuedoaddiction and addiction;"

vi. "It is easy to mistake pseudoaddiction for the real thing. One way to discriminate between psuedoaddiction and addiction is that psuedoaddiction resolves when the patient obtains adequate analgesia; addictive behavior does not."

257. The book, which was paid for by Defendants and widely distributed to doctors, does nothing to support its title. Rather, it downplays addiction, overemphasizes pain treatment as a right while there was no safe solution to treat it, emphasizes falsehoods such as psuedoaddiction, and allays doctor's fears that they could suffer board action related to prescribing opioids. In short, far from teaching responsible opioid prescribing, the book simply delivers the same types of false and misleading messages delivered by Defendants examined above.

9. 2009 APS/AAPM Guidelines

258. Defendants also cited the publication Chou, Roger, et al. "Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain." The Journal of Pain10.2 (2009): 113-130, in their marketing efforts (referred to as the "2009 APS/AAPM Guidelines.")[166]. See Perri Report Schedule 14. That publication, while starting to make some progress toward articulating a better standard for opioid prescribing, was used to dangerously continue to advocate for widespread opioid use to treat chronic pain conditions in the face of no real evidence of efficacy and after over a decade where people in the United States were becoming addicted to and dying from prescription opioids.

259. The Guidelines themselves admit that the "recommendations" regarding chronic opioid therapy were based on "low quality evidence." For example:

> 1.1 Before initiating COT [Chronic Opioid Therapy], clinicians should conduct a history, physical examination and appropriate testing, including an assessment of risk of substance abuse, misuse, or addiction (strong recommendation, **low-quality evidence).**
>
> 1.2 Clinicians may consider a trial of COT as an option if CNCP is moderate or severe, pain is having an adverse impact on function or quality of life, and potential therapeutic benefits outweigh or are likely to outweigh potential harms (strong recommendation, **low-quality evidence**).
>
> 2.1 When starting COT, informed consent should be obtained. A continuing discussion with the patient regarding COT should include goals, expectations, potential risks, and alternatives to COT (strong recommendation, **low-quality evidence**).
>
> 3.1 Clinicians and patients should regard initial treatment with opioids as a therapeutic trial to determine whether COT is appropriate (strong recommendation, **low-quality evidence).**
>
> 3.2 Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment

[166] APS and AAPM sponsored the 2009 Guidelines.

> of therapeutic goals, and predicted or observed harms (strong recommendation**, low-quality evidence).**
>
> 7.1 When repeated dose escalations occur in patients on COT, clinicians should evaluate potential causes and reassess benefits relative to harms (strong recommendation, **low-quality evidence**).
>
> 7.3 Clinicians should consider opioid rotation when patients on COT experience intolerable adverse effects or inadequate benefit despite dose increases (weak recommendation, **low-quality evidence).**
>
> 7.4 Clinicians should taper or wean patients off of COT who engage in repeated aberrant drug-related behaviors or drug abuse/diversion, experience no progress toward meeting therapeutic goals, or experience intolerable adverse effects (strong recommendation, **low-quality evidence**).
>
> 12.1 In patients on around-the-clock COT with breakthrough pain, clinicians may consider as-needed opioids based upon an initial and ongoing analysis of therapeutic benefit versus risk (weak recommendation, **low-quality evidence**).

260. Tellingly, the panel did not rate any of its 25 recommendations as supported by high quality evidence. Only four recommendations were viewed as supported by even moderate quality evidence.

261. Dr. Joel Saper, one of the committee members involved in drafting the guidelines, who resigned out of a concern that they "would lead to serious public safety issues" expressed serious reservations about the contents of the Guidelines and the pharmaceutical companies' influence on their content.[167] As Dr. Saper explained, opioids are unlike other drugs: "They produce dependency, craving, euphoria, major endocrine disturbances and tranquilization, and are more likely to be fatal and harmful than most other day-to-day treatments."[168] And, "when people are maintained on these drugs for very long periods of time, it becomes very difficult to

[167] Joel Saper Dep., p. 34.

[168] *Id.* at 102.

take them off of it…."[169] Thus, Dr. Saper believed that there should be a credentialing pathway before doctors could prescribe opioids long-term for chronic pain, and the committee should not publish criteria to allow any licensed physician to prescribe opioids long-term without "training and experience in the field and knowledge of the drugs themselves."[170] But he was in the "stark minority," his "recommendations were soundly rejected," and there "would be no barriers to prescribing or standards, even self-assessment of competence."[171] Any doctor with "a DEA number could prescribe opioid to any patient without limiting criteria, restrictions, or background considerations."[172]

262. So, Dr. Saper resigned rather than put his name on the guidelines. And in his resignation letter, Dr. Saper made several salient points worth quoting here:

- "By failing to establish pretreatment competence expectations, the guidelines either assume competence or reflect the view that no special knowledge or experience is required to effectively and safely carry out the assessment and treatment of chronic pain patients. I believe that most reasonable authorities would find that indefensible."
- "In my view the guidelines have set the bar so low for initial administration by any physician who has a medical license and DEA number that the guidelines will in fact encourage use by those who are unprepared to carry out the task responsibly and safely."

[169] *Id.* at 22.

[170] *Id.* at 18, 34.

[171] *Id.* at 27, 112.

[172] *Id.* at 112.

- "We should know better. Chronic pain does not compel an emergency response as might be argued by the case of acute pain. Diligent training and competence should be prerequisites to the chronic administration of opioid therapy. These guidelines do not advance this principle."[173]

263. Dr. Saper also commented on how "narcopharma" money influenced the guidelines, writing that "Such guidelines, developed with the support of industry and by many who have been personally paid large sums by industry, create a nexus that will not be ignored."[174]

10. 2009 AGS Guidelines

264. Defendants also cited the publication The Pharmacological Management of Pain in Older Persons published by the American Geriatric Society in their marketing efforts (referred to as the "2009 AGS Guidelines"). *See* Perri Report Schedule 14. As per *supra* Section IV.I.6, the American Geriatric Society was funded by Defendants. Like their 2002 Guidelines, the 2009 Guidelines contained statements that were inaccurate and irresponsible for Defendants to distribute or use in sales or marketing.

265. For example, this publication contained the following statements that:

[173] Saper Dep., Ex. 3.

[174] *Id.* at 94 and Ex. 3. Or as Dr. Saper explained, "opioids are not like some of the other drugs which have a whole different profile and safety margin. Not that it makes it better one way or the other, but the risk is that advocacy for those drugs has to be based on medical common sense independent of the financial flow of dollars, and it was my growing fear that that was not the case in the case of these guidelines…. I felt -- still do -- that with opioids, they were penetrated in a much more intense way and that we were dealing with a much more potentially dangerous product that needed to be handled much more independently of people with a vested commercial interest." *Id.* at p. 45-47.

a. "Any pain complaint that affects physical function or quality of life should be recognized as a significant problem. Older patients with functional impairment or diminished quality of life are candidates for pharmacological therapy;"

b. "Controlled trials have established the efficacy of various opioids in the treatment of persistent pain associated with musculoskeletal conditions, including osteoarthritis, and low back pain, and the management of several neuropathic pain conditions, such as diabetic peripheral neuropathy and postherpetic neuralgia;"

c. "Although the risks [of addiction] are exceedingly low in older patients with no current or past history of substance abuse, it is impossible to identify every patient who will abuse or divert prescribed opioids."

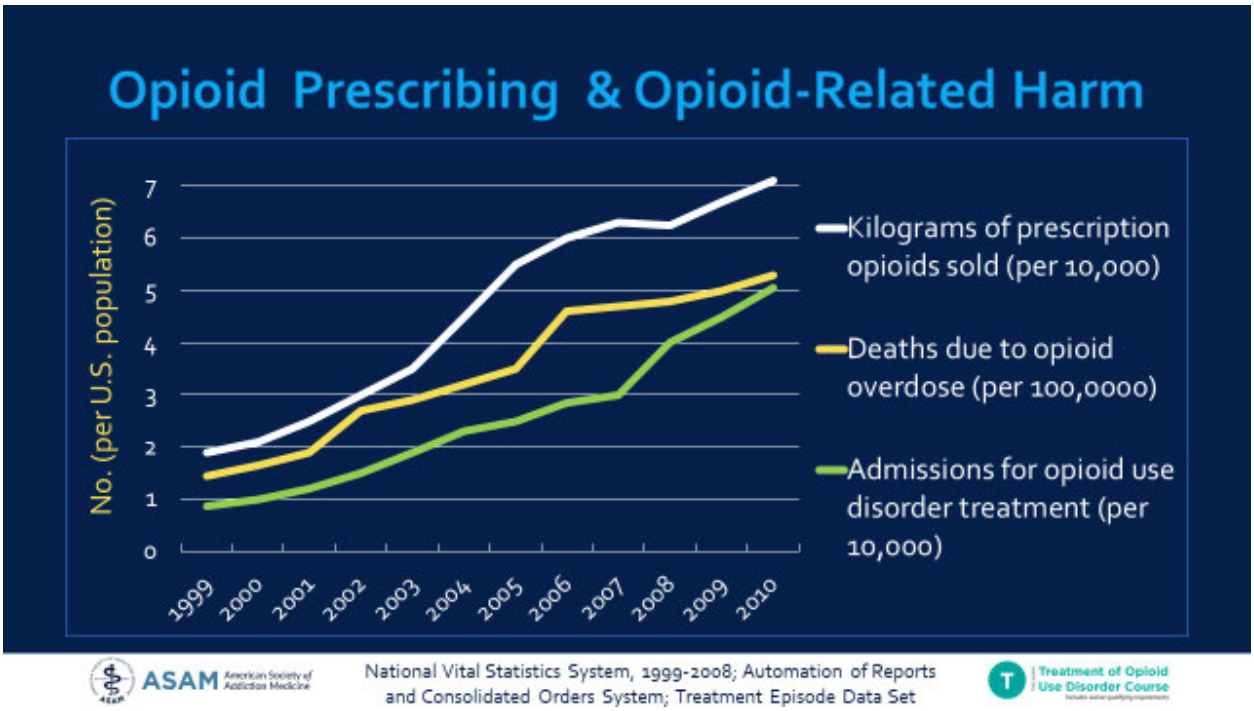
266. Again, this emphasizes non-existent controlled trials demonstrating the efficacy of chronic opioid agonist therapy, and re-enforced the total myth that the risk of addiction is low in older adults.

J. Exposure Caused Harm: The Epidemic

267. Defendants caused a large population of people throughout the United States, in Ohio and in Cuyahoga and Summit Counties, to be exposed to prescription opioids.

268. That exposure caused serious harm, both across the United States and, most acutely and severely, in Ohio and the surrounding region.

269. The direct link between exposure and harm is starkly illustrated by the following graphic:



270. The numbers are catastrophic:

i. In 2017, approximately 48,000 Americans died of an opioid overdose, including those from prescription opioids, heroin and synthetic opioids such as fentanyl.

ii. Based upon opioid overdoses, for the first time in over 25 years, the life expectancy in the United States has fallen.[175]

iii. Data shows that over 1 million people (likely a low estimate) suffer from a heroin/fentanyl use disorder, with most of these stemming from an initial addiction to prescription opioids (over 75%). [176]

[175] U.S. Dept. of Health and Human Service, Nat'l Ctr. for Health Statistics, Health, United States, 2017: With Special Feature on Mortality (2018).

[176] JAMA Psychiatry. 2014 Jul 1;71(7):821-6. doi: 10.1001/jamapsychiatry.2014.366. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. Cicero TJ1, Ellis MS1, Surratt HL2, Kurtz SP2.

iv. At least 13 million people in the US have some level of opioid misuse and use disorder. [177]

v. It is estimated that in 2015, 92 million US adults (38%) took a prescribed opioid. Up to 29% of these patients likely misused them (26.6 million)[178]

271. According to the CDC, drug poisoning deaths in the United States now exceed deaths from motor vehicle accidents, firearms, homicides and suicide:[179]

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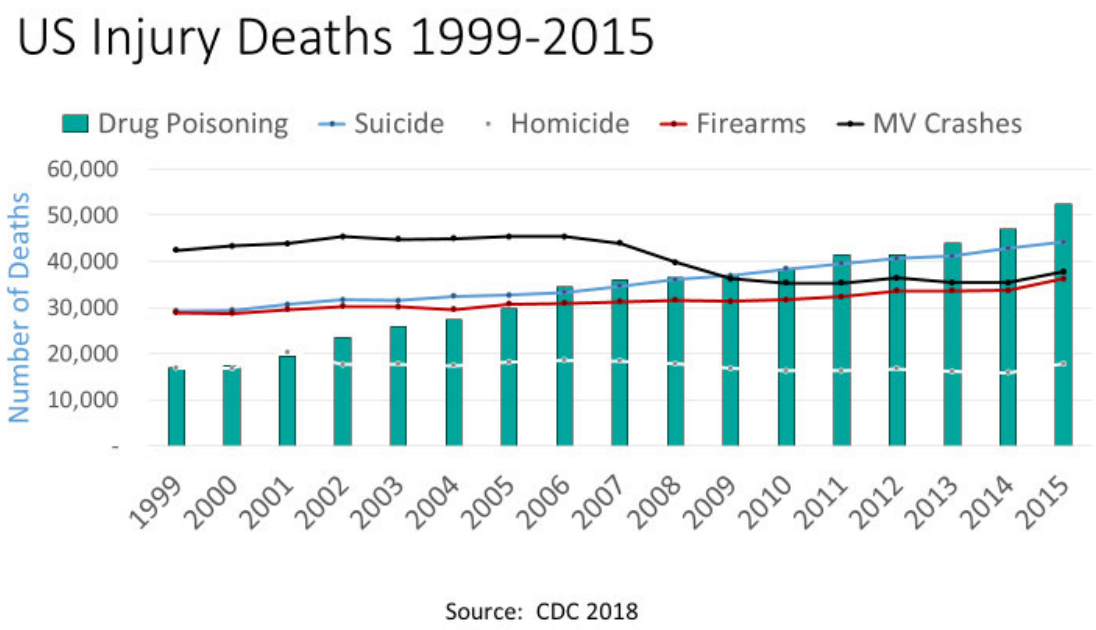
[177] https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2017/NSDUHDetailedTabs2017.htm#lotsect1se (tables 7.2, 7.28, and 7.34)

[178] https://www.reuters.com/article/us-health-opioids-prescriptions-idUSKBN1AG2K6 Pain. 2015 Apr;156(4):569-76. doi: 10.1097/01.j.pain.0000460357.01998.f1. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis.

Vowles KE1, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN.

[179] CDC Guideline, *supra* note 1.



272. The nation has now witnessed the broadest and deepest opioid epidemic in history.

273. For the first time, this opioid epidemic hit small town and rural areas of the nation harder than urban areas and affected all socioeconomic and demographic groups.[180] It is dramatically affecting youth and young adults (ages 18-25).[181]

[180] Theodore J. Cicero et al., *The Changing Face of Heroin Use in the United States: A Retrospective Analysis of the Past 50 Years*, 71 JAMA Psychiatry 7, 821 (2014), doi:10.1001/jamapsychiatry.2014.366.

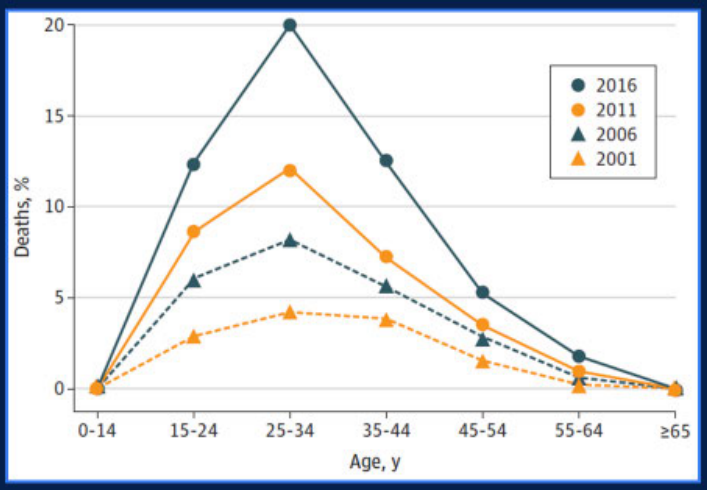
[181] Gomes T, et al. JAMA Network Open. 2018; 1(2):e180217; Samet JH, Kertesz SG. JAMA Network Open. 2018;1(2):e180218; https://www.drugabuse.gov/related-topics/trends-statistics/infographics/abuse-prescription-rx-drugs-affects-young-adults-most (Source NSDUH 2015

Proportion of Young Adult Deaths Related To Opioids

Between 2001—2016, opioid-related deaths increased by 345%

Aged 15 to 24 yrs, 12.4% of deaths were attributable to opioids in 2016

- greater than 3-fold increase from 2001 to 2016
- alcohol, cocaine, or benzodiazepines were also present in 45% of deaths



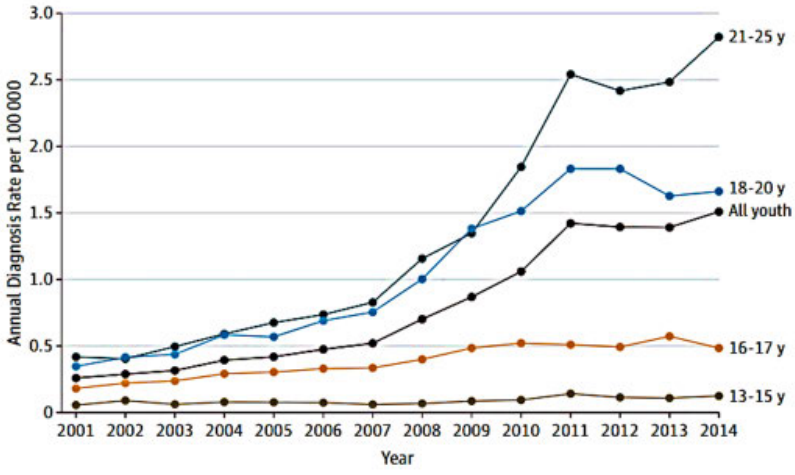
ASAM American Society of Addiction Medicine

Gomes T, et al. JAMA Network Open. 2018;1(2):e180217
Samet JH, Kertesz SG. JAMA Network Open. 2018;1(2):e180218

Treatment of Opioid Use Disorder Course

Trends in New OUD Diagnoses Among Youth and Young Adults

The diagnosis rate of OUD increased nearly 6-fold from 2001 to 2014 (from 0.26 per 100 000 person-years to 1.51 per 100 000 person-years).



274. In 2017 alone, at least 11.4 million people aged 12 or older misused opioids.[182] This number represents 4.2 percent of the population aged 12 or older.[183] About 769,000 adolescents aged 12 to 17 misused opioids in the past year.[184] This number corresponds to 3.1 percent of adolescents who misused opioids in the past year.[185] About 2.5 million young adults aged 18 to 25 misused opioids in the past year, which corresponds to about 7.3 percent of young adults.[186] An estimated 8.1 million adults aged 26 or older misused opioids in the past year, which represents 3.8 percent of adults in this age group.[187]

[182] Substance Abuse and Mental Health Admin., *Key Substance Use and Mental Health Indicators in the United States: Results from the 2017 National Survey on Drug Use and Health* (2018), https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHFFR2017/NSDUHFFR2017.pdf.

[183] *Id.*

[184] *Id.*

[185] *Id.*

[186] *Id.*

[187] *Id.*

Figure 21. Past Year Opioid Misuse among People Aged 12 or Older, by Age Group: 2017

Note: Opioid misuse is defined as heroin use or prescription pain reliever misuse.

275. In 2017, the number of recent initiates of prescription pain reliever misuse (2.0 million) was the second highest among the illicit drugs, after the number of marijuana initiates.[188] The number of people aged 12 or older who misused prescription pain relievers for the first time in the past year averages to about 5,500 initiates per day.[189] In 2017, approximately 316,000 adolescents aged 12 to 17 misused prescription pain relievers for the first time in the past year.[190] This number averages to approximately 900 adolescents each day who initiated prescription pain reliever misuse.[191] An estimated 465,000 young adults aged 18 to 25 and 1.2

[188] *Id.*

[189] *Id.*

[190] *Id.*

[191] *Id.*

million adults aged 26 or older initiated prescription pain reliever misuse in the past year.[192] These numbers average to about 1,300 young adults and about 3,400 adults aged 26 or older each day who initiated prescription pain reliever misuse [193]

276. These statistics are only part of the story. Indeed, we have seen a population of people destroyed by opioids, where the drugs became the driving factor in people's lives. Over and over we have seen people exposed to these powerful drugs spiral out of control to the point where their lives revolve around avoiding withdrawal by finding the next pill or fix that will prevent it, by legal or illegal means. Throughout the epidemic we have seen people who are addicted to opioids lose all logic and even self-interest to their drive to use these drugs. It has destroyed not only these individuals, but their families and the communities who must now take care of them. This includes children with drug addicted parents, a court system flooded by opioid related offenses, emergency departments and county coroner offices overwhelmed by overdoses and deaths and an increase in drug related crime. There is almost no area of a community these problems do not touch.

1. The Epidemic in Cuyahoga and Summit Counties

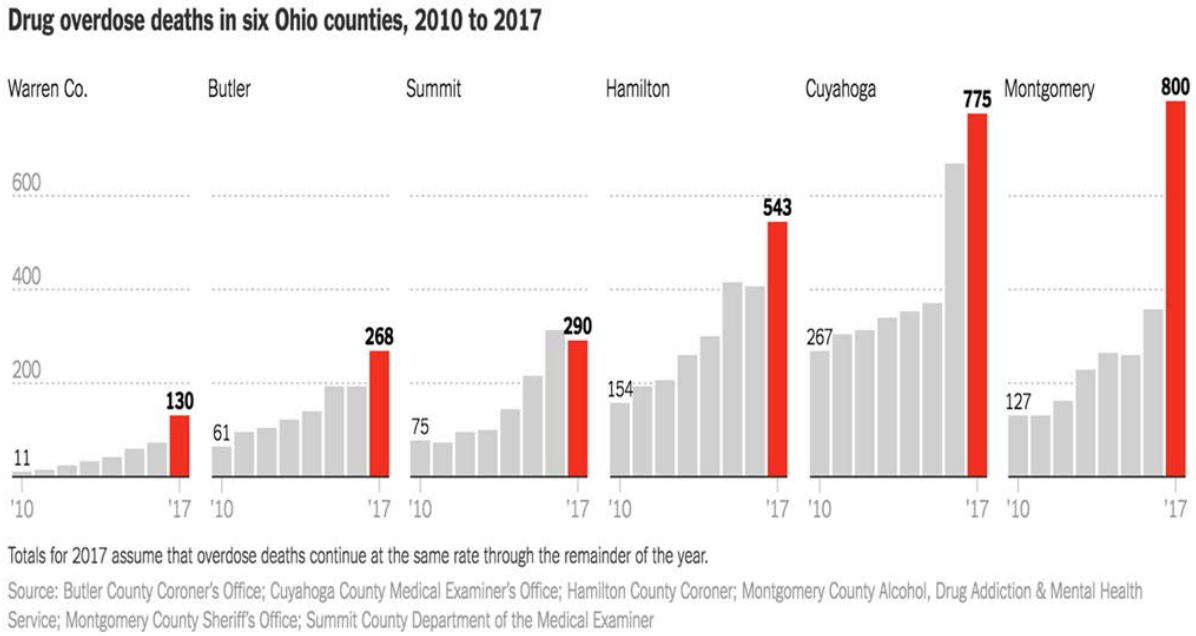
277. All of these problems of the nationwide epidemic have manifested themselves in Ohio and in Summit and Cuyahoga Counties. Indeed, Ohio has been the second-hardest hit state in the nation.[194] Thirteen thousand and fifty-nine people have died from opioid overdose in Ohio

[192] *Id.*

[193] *Id.*

[194] NIH, Opioid-Related Overdose Deaths – Ohio, Drug Abuse.Gov (Feb. 2018), https://www.drugabuse.gov/drugs-abuse/opioids/opioid-summaries-by-state/ohio-opioid-summary.

just between 2010 and 2016.[195] Cuyahoga County and Summit Counties suffered a devastating number of overdose deaths:[196]



278. But, as seen across the United States, overdose deaths are just part of the problem. Cuyahoga and Summit Counties have been overwhelmed by the costs to the community of

[195] The Ohio Alliance for Innovation in Population Health (OAIPH). Opioid overdose responsible for over 500,000 years of life lost in Ohio, Ohio University Compass (June 14, 2018), https://www.ohio.edu/compass/stories/17-18/06/opioid-overdose.cfm.

[196] *Opioid Epidemic*, Public Children Services Association of Ohio (PCSAO), http://www.pcsao.org/programs/opiate-epidemic; Jen Steer, *Summit county executive declares state of emergency over opioids crisis*, Fox 8 Cleveland (Oct. 25, 2017), https://fox8.com/2017/10/25/summit-county-executive-declares-state-of-emergency-over-opioid-crisis/; *Be Well Special: Exploring the Impact of the Opioid Crisis on NE Ohio*, Ideastream (Jan. 17, 2018), https://www.ideastream.org/programs/be-well/be-well-special-exploring-the-impact-of-the-opioid-crisis-on-ne-ohio; Cty. of Summit Alcohol, Drug Addiction & Mental Health Serv. Bd., *Recovery. It's Worth the Fight: Addiction Resource Guide* (2017), https://www.summitcountyaddictionhelp.org/Data/Sites/19/pdfs/adm-board-addiction-resource-guide.pdf.

opioid addiction, misuse and dependence and the resultant impacts on family services, the criminal justice system, law enforcement and almost every area of County services.

279. I have been provided with testimony and information from both Cuyahoga and Summit Counties regarding the various impacts on their communities (summarized in this Section). These facts are consistent with my own experience in Northeast Ohio and the facts I have learned through consulting with various government entities, opioid task forces and organizations working to combat the opioid epidemic in Ohio.

a. Cuyahoga County

280. Cuyahoga County has been dramatically impacted by the opioid epidemic, and drug overdose is now the leading cause of accidental death.[197] In 2015, one person died every day in Cuyahoga County from a drug overdose.[198] During January and February of 2016, one person died every day in Cuyahoga County from a heroin or fentanyl overdose.[199] Specifically, January set a record for fentanyl deaths that was then broken in February.[200] Thereafter, in March of 2016, two people died every day in Cuyahoga County from a heroin or fentanyl overdose.[201] From 2006 until 2016, over 1,000 people died in Cuyahoga County from opioid overdoses.[202]

281. In the year 2016 in Cuyahoga County, there were 666 drug overdose deaths reported by the Cuyahoga County Medical Examiner's Office.[203] In 2017, the emergency rooms treated an estimated 9,191 patients presenting with drug related injuries, a 21% increase

[197] *See* CUYAH_014188900.

[198] *See* CUYAH_014361009.

[199] *Id.*

[200] *Id.*

[201] *Id.*

[202] *See* CUYAH_014362277; CUYAH_014362278.

[203] *Id.*

compared to 2016.[204] Indeed, the number of deaths linked to prescription drug abuse increased by almost 500% from 1999 to 2013.[205] Moreover, heroin mortality rose significantly, from 40 deaths associated with heroin in 2007 to 161 in 2012.[206] Alarmingly, approximately 75% of the people who were dying of heroin overdoses had a previous prescription for opiates.[207] In other words, within two years of death, almost 3 of 4 heroin fatalities had received a legal prescription for a controlled substance.[208] The crippling effect of this public health emergency is felt across all facets of Cuyahoga County's government.

282. In 2015, Cuyahoga County's Department of Children and Family Services (DCFS) experienced an uptick in the number of children in placement. Moreover, the number of abuse, dependency, and neglect cases in juvenile court increased.[209] As of 2017, 32% of removals were due to drug or alcohol related reasons.[210] In 2017, there were 2,000 children and teens in temporary or permanent custody, the highest since 2011.[211] Over the past few years, there was a 62% increase in drug-exposed infants.[212] In 2016, 483 drug-exposed children were

[204] *See* CUYAH_000018578.

[205] *Id.*

[206] T. Gilson 30(b)(6) Dep. Ex. 10 at 1.

[207] *See* H. Shannon Dep. Tr. 26:16-28:2; 28:17-28:23; 36:7-37:21; T. Gilson 30(b)(6) Dep. Tr. 251:9-254:1; 314:22-315:15.

[208] T. Gilson 30(b)(6) Dep. Ex.10 at 13, produced natively at CUYAH_001397330.

[209] M. Keenan Dep. Tr. 371:4-372:2.

[210] CUYAH_002351018.

[211] *Id.*

[212]See CUYAH_002462640; CUYAH_002462920

referred to Sobriety Treatment and Recovery Teams (START).[213] In 2017, that number grew to 523.[214] The START program has also seen an increase in opiate-related cases and referrals, including almost 100% of the Family Drug Court population.[215]

283. The opioid epidemic has resulted in increased average daily population at the county jails and escalation in the costs associated with medical care for opiate addicted inmates.[216] The Cuyahoga County Corrections Center provides housing and MAT for 26,000 inmates annually.[217] Seventy-five percent of these inmates have a substance use disorder. In 2016, almost 30% of the Common Pleas Court defendants had an opioid diagnoses.[218] The Sheriff's Office has also felt the impact, experiencing a growth in costs due to more inmates, deputy sheriff overtime and transportation expenses.[219] In addition, the Juvenile Court, Prosecutor's Office, and Public Defender's office have been overburdened with increased caseloads and associated costs.[220] Moreover, 85% of the participants in the Drug Court have an opioid use disorder.[221] Since the Drug Court started in May of 2009, they have expanded to keep

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[213] See CUYAH_002462638; 002462640; CUYAH_002462641, CUYAH_002467830.

[214] CUYAH_002486141.

[215] CUYAH_002462932.

[216] M. Keenan 30(b)(6) Dep. Tr. 48:15-50:5; 114:19-21.

[217] CUYAH_003505168.

[218] *Id.*

[219] M. Keenan 30(b)(6) Dep. Tr. 114:4-18.

[220] *See, e.g.*, M. Keenan 30(b)(6) Dep. Tr. 33:17-35:2; 113:3-8; 135:17-136:10.

[221] M. Leckler Dep. Tr. 59:20-60:16; 249:7-256:22.

up with the overflow stemming from the opioid epidemic, hiring additional probation and case management staff.[222] Additional costs have also been incurred, including, for example, drug testing and treatment costs (e.g., residential and intensive outpatient), transportation costs (e.g., bus tickets), medical costs (e.g., MAT), and costs associated with referrals from county jails.[223] An additional docket was created to deal specifically with opioid use disorder.[224]

b. Summit County

284. The opioid epidemic has devastated Summit County.[225] On October 25, 2017, Summit County declared a countywide emergency due to the opioid epidemic.[226] This declaration is still in effect today as Summit County remains in the grips of a public health crisis.[227] The opioid epidemic has resulted in an unprecedented loss of life in Summit County.[228]

285. In 2014, 32% of hospital admissions in Summit County had a primary diagnosis of opiate use disorder.[229] The Summit County Opiate Task Force was formed in response to the

[222] *Id.* at 348:23-351:25; 391:4-393:18.

[223] *Id.*

[224] *Id.*

[225] Skoda (Health Commissioner, Summit County Public Health) Dep. Tr. 370:20-23.

[226] Emergency Proclamation, SUMMIT_001266515.

[227] Skoda Dep. Tr. 367:3-11.

[228] ADM 2016 Annual Report at 2, SUMMIT_001084697.

[229] *Unduplicated Admissions for Opiate Abuse and Dependence* (2015), https://mha.ohio.gov/Portals/0/assets/Research/Maps/Ohio_MACSIS_2014_v6.pdf.

rising number of opiate related treatment admissions and deaths.[230] Acute withdrawals led to over 1,500 detoxifications at the ADM Crisis Center, a majority of which were opiate related.[231] At the time that the Task Force was created, Summit County's Alcohol, Drug Addiction and Mental Health Services Board reported that although heroin was stronger and less expensive than it, 45% of opiate dependent persons being admitted to treatment were addicted to prescription opioids.[232] The number of babies born to opioid addicted mothers with NAS diagnoses was also increasing.[233] Summit County also had one of the highest rates of naloxone administration rates in the state in 2014, with an estimated 24.6 naloxone administrations per 10,000 persons during this time.[234] Unintended drug overdoses were rising, increasing numbers of inmates were experiencing drug withdrawals in jail; there were increases in heroin and prescription drug related arrests; diversion of prescription medications was increasing and there was an increase in

[230] February 5, 2014 Invite to Key Community Stakeholders re: Inaugural Convening of the Summit County Opiate Task Force, Summit_001090233; Kohler Dep. Tr. at 222:2-22 (reporting 144 overdoses in 2014).

[231] *Id*.

[232] *Id*.

[233] *See* August 20, 2014 Opiate Task Force Health Care Subcommittee Minutes, Summit_001191837 (reporting 10% of NICU admissions had NAS diagnoses and the number of patients with NAS was increasing). *See also* May 4, 2015 Opiate Task Force Quarterly Stakeholders Meeting Minutes, SUMMIT_ 001020273 (reporting that local data shows NAS is more common in Akron than anywhere in Ohio and that average length of stay of 17 days with a peak of 53 days).

[234] *Naloxone Administration in Ohio* (2015), https://mha.ohio.gov/Portals/0/assets/Research/Maps/Admin_Rate_2014.pdf.

hepatitis diagnosis.[235] In his convening invite, ADM's Executive Director Jerry Craig, further explained:

> We are being impacted in every segment of our community; health care, public health, courts, law enforcement, pharmacy practice, addictions treatment, employment, faith and family.

286. In 2015, Summit County experienced 212 total overdose deaths and by 2016 overdoses deaths dramatically increased to 336 deaths.[236] The continued rise in the death continued to rise in 2016 necessitating the Summit County Medical Examiners use of the State's mobile morgue.[237] Overdose death rates were reported daily and Summit County was experiencing a "loss of a sense of community" and an "overwhelming sense of hopelessness."[238] Emergency rooms visits skyrocketed in 2016 with 2433 overdoses as compared to 595 in 2012.[239]

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[235] SUMMIT_001090233.

[236] Emergency Proclamation, SUMMIT_0012266515; *see also* Kohler Dep. Tr. 51:19 – 53:6 (testimony from Summit County Medical Examiner, stating there were 213 overdose deaths between January 1 of 2015 and December 31st of 2015).

[237] Amani Abraham, *Mobile Morgue Trailer Brought Into Summit County To Deal With Surge of Overdoses*, WKYC3 (June 27, 2017 12:48 P.M.), https://www.wkyc.com/article/news/local/akron/mobile-morgue-trailer-brought-into-summit-county-to-deal-with-surge-of-overdoses/452444686.

[238] Greta Johnson 30(b)(6) Dep. Tr. 192:11-194:12.

[239] Summit County Public Health, Dashboard for Estimated Overdose Emergency Room Department Visits 2016-2019 (reporting that since 2012, Summit County has experienced 178,234 emergency room drug overdoses).

287. The opioid epidemic has overloaded many of Summit County's systems and impacted all parts of the community.[240] In particular, the epidemic has been disproportionately felt by treatment providers, first responders, hospitals, Children Services, the criminal justice system, the Medical Examiner, and the families of Summit County.[241] As the number of opiate-related deaths and overdoses grew, first responders became overwhelmed and entire workforces were affected.[242] The opioid crisis has been an "absolute total devastation" for people witnessing repeat overdoses and dealing with the sheer volume of calls.[243]

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[240] Kim Patton (Addiction, Prevention and Training Coordinator, Summit County ADM) Dep. Tr. 269:19 -271:1 ("[M]any of our systems were becoming overloaded, whereas Summit County Children Services was taking in kids beyond capacity, whether it's because children lost their caregivers to overdose, or if they were in the criminal justice system. We also had mobile morgues delivered and set up within our county at that time, and we were getting calls at the ADM Board at that time, in that -- those summer months of 2016, where people were fearful, calling. I had one individual, a family member call, indicating their family member overdosed four times, and how can they just get them into treatment because they don't want them to die. So as far as Summit County specifically, it really wasn't -- it was when I first became employed with the ADM Board and was working with the ADM Board."). *See also* Tucker Dep. Tr. 142:17 – 143:24 ("The opiate issue . . . just seemed to raise to the level of just overwhelming our ability to respond. [Other drugs] never overwhelmed our resources like this opiate issue has . . . to the point where it has been really stressing our resources, our ability to respond, overwhelming our personnel."); Summit Cty. Pub. Health, *Population Health Vital Statistics Brief, Volume 3: Drug Overdoses, July1- July 31 2018*, SUMMIT_001631090 - SUMMIT_001631098 ("A 'community-crisis,' it has impacted 'all parts of the community; city and suburban, white and black, male and female, young and old.'").

[241] 2016 ADM SSAB Annual Budget Review, SUMMIT_001215295.

[242] Julie Barnes, Executive Director, Summit County Children Services, Dep. Tr. 162:10-164:9:

> There's been a tremendous impact on the entire workforce related to the opiate epidemic. I have personally talked to supervisors and staff who have experienced very significant trauma when they've lost a child who may have got into a parents' drugs and overdosed. We've had some die. We've had parents who've died. We have parents who relapse. It's very hard on a worker if you're working with a case and the family is doing well and you're close to feeling like you can be able to send this child back to live with their family, and then the parent relapses, and they're unable to make that reunification. There's a sense of failure that goes with that when someone fails or

288. In 2014, Summit County Children Services (SCCS) saw an increase in the need for services based on the use of heroin, opiates or opioids.[244] There had been a steady increase in demand for services since 2012, and in 2016, Summit County Children Services was taking in an unprecedented number of children who lost their caregivers to overdose or to the criminal justice system.[245] SCCS found itself in the middle of the opioid crisis.[246] SCCS found itself in the middle of the opioid crisis.[247] Julie Barnes, Executive Director of Children Services, testified that in her 28 year career "dealing with opiates has been one of the greatest challenges that we've

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> someone dies or someone is harmed. And relapse is very high. Overdoses are very high. So those have a very traumatic impact on the staff.

See also Johnson 30(b)(6) Dep. Tr. 195: 2-18 (explaining how "compassion fatigue" is occurring with first responders and treatment providers and need for resources to make sure they are supported and don't become "overwhelmed by hopelessness" and "overwhelmed by the sheer volume and turn cold to it.").

[243] Tucker Dep. Tr. 262:3–263:3.

[244] Julie Barnes Dep. Tr. 88:22-89:16; 92:19-93:13.

[245] Patton Dep. Tr. 269:19 -271:1.

[246] *Id*.

[247] Summit Cty. Children Serv., 2016 Annual Report, SUMMIT_000043051 (noting that the average number of children in custody in 2012 was 558 and increased each year to 685 in 2016.) *See also* Barnes Dep. Tr. 372:5-373:6 ("I have many examples of [and] very specific situations where I know that children have been harmed. I know their parents have overdosed frequently. I know that my caseworkers have struggled with [ ] telling a child that their parent is deceased. Removing a child from a home because their parents have addiction issues and the trauma of removal alone is a significant trauma for children."); Barnes Dep. Tr. 281:18-284:9; 162:10-164:9 (describing the need for more resources and staffing due to the fact that cases are too complex for the current caseloads; need to have more foster homes, clinical person on staff to work with caseworkers, trauma expert to deal with childhood trauma and long term impact and secondary trauma involving first responders, more training, more resources and more support for kinship programs.

had with our clientele."[248] SCCS saw a drastic increase in the number of referrals, a 17% increase in number of children who entered custody and an 18% increase in the cost of placing and caring for children affected by substance abuse. It has created an urgent need for more foster and adoptive homes.[249] In 2017, SCCS continue to see the impact of the opioid epidemic on the children and families they serve by the increasing number of children in custody.[250] There are still children coming into Children Services at higher rates than before.[251]

289. Law enforcement and the courts were impacted by increased caseloads. For example, Summit County' Adult Probation Department created the Opiate Unit for low and moderate risk offenders to combat the growing percentage of opiate addicted individuals who came through the department and address the specialized needs of the opiate user. The Opiate Unit provides intensive supervision services upfront and provides linkage and coordination to community treatment providers. Officers were added due to the growing opiate epidemic and attended specialized training to work with this population.[252] Drug Courts have had to increase

[248] Barnes Dep. Tr. 71:6-72:3.

[249] Summit Cty. Children Serv., 2016 Annual Report, SUMMIT_000043051.

[250] Summit Cty. Children Serv., 2017 Annual Report, SUMMIT_002052855.

[251] Greta Johnson 30(b)(6) Dep. Tr. 258:10-11.

[252] Summit Cty. Court of Common Pleas, 2016 Annual Report, 34, SUMMIT_000004286 (noting that during 2016, there were 429 cases placed in this specialty unit). *See also* Jeffery Sturmi (Deputy Chief Probation Officer) Dep. Tr. 136:8-139:5 (started to see increases in 2012 "when courts, treatment agencies started to identify more and more clients coming to their attention for having opiate use disorder that was exacerbated by overdose").

their capacity and expand to cover crimes that were committed as a result of addiction and drug seeking behaviors.[253]

290. Although capacity for treatment has been expanded and the County has worked to streamline the process residents into services more quickly, the need for treatment outstrips available resources.[254] Today, Summit County is faced with a population of people who are living with addiction.[255]

2. Illicit Drugs and Diversion Were a Foreseeable Consequence of Exposure to Prescription Opioids

291. As outlined in the prior two Sections, Summit and Cuyahoga Counties have experienced a devastating and increasing problem in recent years with illicit opioids, including heroin, fentanyl and carfentanil.

292. As observed by the National Academies of Science and Medicine in their 2017 Consensus Report, "overdose deaths from illicit opioids (including heroin and synthetic opioids such as fentanyl) nearly tripled during this time period [2011-2015], driven in part by a growing number of people whose use began with prescription opioids."[256] The NASEM went on to conclude that "the prescription and illicit opioid epidemics are intertwined; indeed, a majority of heroin users report that their opioid misuse or OUD began with prescription opioids. In addition, the declining price of heroin, together with regulatory efforts designed to reduce harms

[253] Greta Johnson 30(b)(6) Dep. Tr. 246: 2 – 247:6.

[254] Gerald Craig (Executive Director of Summit County ADM) Dep. Tr. 271:13-272:7; *see generally* Kim Patton Dep. Tr.

[255] Johnson 30(b)(6) Dep. Tr. 257:22-23.

[256] NASEM, *Pain Management and the Opioid Epidemic*, *supra* note 62.

associated with the use of prescription opioids (including the development of abuse-deterrent formulations [ADFs], may be contributing to increased heroin use."[257]

293. With an increase in exposure to prescription opioids, both the diversion of prescription opioids to illegal use,[258] and an increase in the supply of illegal opioids like fentanyl and heroin, were utterly foreseeable.

294. Additionally, data has shown that approximately 70-80% of heroin users in the last 20 years started their opioid use with prescription opioids.[259] This inevitably led to the increase in fentanyl-related mortality, as the heroin supply has been contaminated with illicit fentanyl.[260]

295. When a population is addicted to prescription opioids, the consumers of the drugs develop a compulsion for those drugs which has to be satisfied.

296. The compulsion caused by the increased exposure to prescription opioids inevitably was satisfied by several illicit methods as well as legal methods (1) pain clinics, pill mills and internet pharmacies, and (2) increased supply of heroin, fentanyl and carfentanil. Pill mills cropped up throughout northeast Ohio. During the 2000s, I helped the government prosecute several pill mill doctors for diversion of prescription opioids to illegal use. But while

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[257] *Id.* at 6.

[258] Volkow, *supra* note 25 at 1253 *citing* A. Shei et al., *Sources Of Prescription Opioids Among Diagnosed Opioid Abusers*, 31 Current Med. Research Op. 779 (2015); C.E. Keller et al., *Practices, Perceptions, And Concerns Of Primary Care Physicians About Opioid Dependence Associated With The Treatment Of Chronic Pain*, 33 Substance Abuse 103 (2012).

[259] Cicero, *supra* note 183, at 821-826.

[260] Christopher M. Jones et al., *Changes in Synthetic Opioid Involvement in Drug Overdose Deaths in the United States, 2010-2016*, 319(17) JAMA Psychiatry 1819 (2018), doi:10.1001/jama.2018.2844.

significant, the pill mills were not responsible for the wide scale exposure of the population to the drugs. The epidemic we see today did not arise just out of pill mills or "bad doctors."

297. And, many of the pill mills and "bad doctors" were, or should have been, known to Defendants in this matter. For example, I was an expert witness in the prosecution of Dr. Adolph Harper, a Summit County practitioner. From at least September 2009 through May 2012, Dr. Harper and his staff were essentially operating a pill mill—distributing hundreds of thousands of doses of opioids to pain patients, many of whom exhibited clear signs of drug addiction. At least eight of Harper's patients died of opioid-related overdoses. Prior to his prosecution and guilty plea, based on documents I have reviewed, it is clear that Dr. Harper was visited hundreds of times by drug representatives from various manufacturers who misrepresented the safety and efficacy of opioids and who were or should have been aware of his inappropriate prescribing.

298. Along with prescription opioids, the heroin and fentanyl supply also spiked. Even when prescribing was still increasing, the appetite of the addicted and dependent outstripped the dramatically increased levels of prescribing. Simple drug economics took over. Heroin is cheaper than prescription opioids. Indeed, where before prescription opioids were the choice of drug, people hooked on pills turned to heroin and fentanyl because it was cheaper and more potent.

299. Then starting in 2010-2013, restrictions on prescribing began to be put in place. The government started to shut down the pill mills. Supply of prescription opioids was restricted as state laws and regulations changed and newer guidelines and standards went into effect to address the crisis. Ever increasingly, those who were addicted to and dependent on prescription opioids transitioned to heroin, fentanyl and carfentanil.

300. As a result of a shift to these even higher potency drugs, mortality spiked again, with devastating impact on Cuyahoga and Summit Counties.

K. Evidenced Based Solutions

301. There can be no disagreement that any approach to resolving the current opioid epidemic should be multi-faceted.

302. At a minimum, solutions must be crafted in the following areas (as well as others):

a. Treatment;

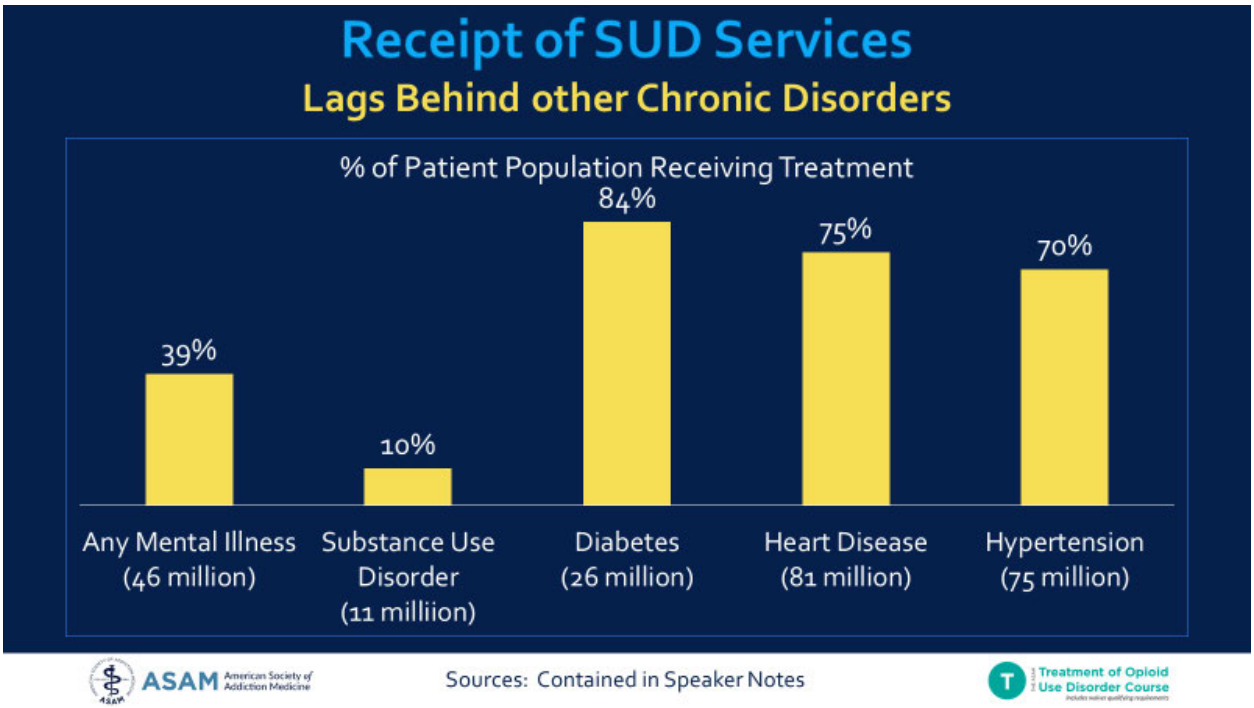
b. Harm reduction

c. Prescriber education.

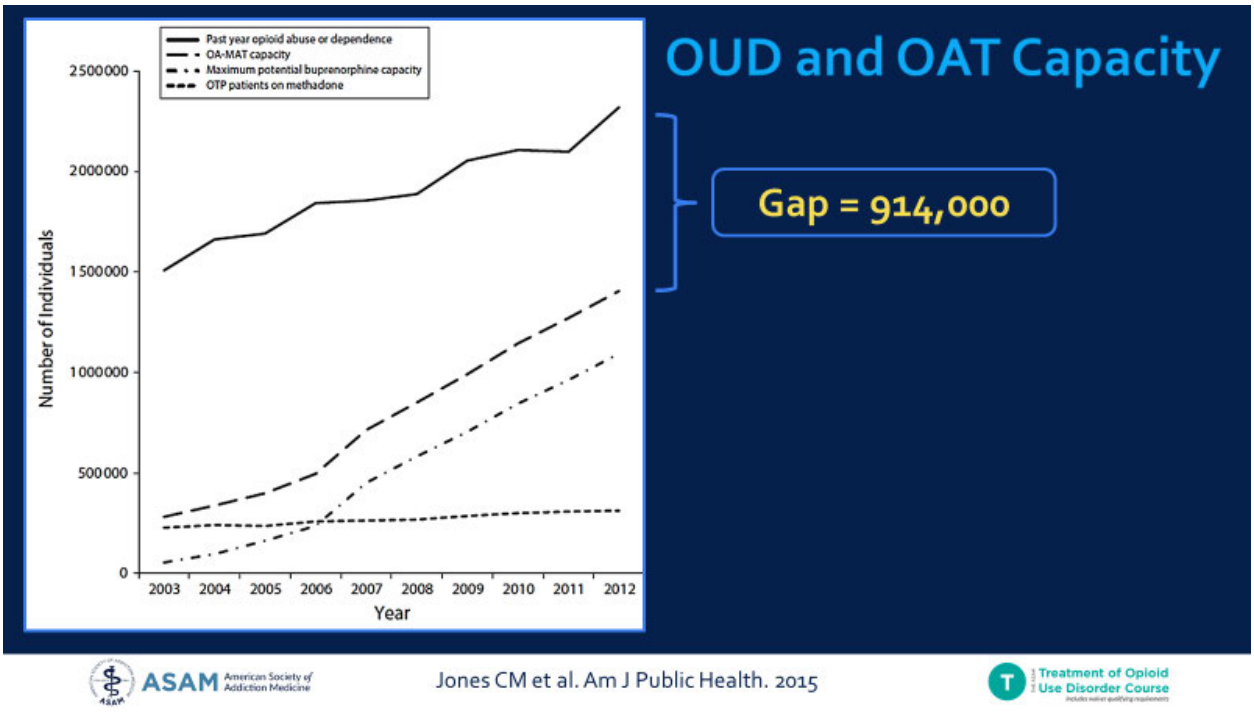
1. Treatment

303. While a "cure" for opioid addiction is unlikely, long-term treatment can limit the disease's adverse effects, reduce the chance of fatality and improve the patient's day-to-day life and ability to function.

304. The current addiction treatment ecosystem is insufficient to handle the volume of addicted, misusing and dependent patients in the United States today. It is estimated that in any given year, only about 18% of people with SUD have received any treatment; only 50% of those (~10% of total) received treatment in a specialty center.



305. For example, one study measured the gap in treatment as follows:



306. This analysis does not include the fact that OUD is likely undercounted, and it makes no mention of the number of patients with misuse and dependence who will require some level of intervention.

307. While current resources are lacking, there is a standard course of treatment that can and should be implemented to treat patients suffering from opioid use disorder. Those standard treatment methods are endorsed by the following organizations and have been proven to be effective in treating patients suffering from opioid use disorder:

i. ASAM (American Society of Addiction Medicine)

ii. SAMHSA (Substance Abuse and Mental Health Services Administration)

iii. NIDA (National Institute on Drug Abuse)

iv. AAAP (American Academy of Addiction Psychiatry)

v. The following sections will cover the standard medical practice for treatment of opioid use disorder and the evidence base for those solutions.

308. The necessary interventions are addressed through three key components of treatment:[261]

- Medical Treatment (including MAT - buprenorphine, methadone and naltrexone) including withdrawal management and ongoing medication.[262]

[261] NASEM, *Pain Management and the Opioid Epidemic*, *supra* note 62, at 230-239.

[262] *Id.*; *see also* American Society of Addiction Medicine (ASAM), *National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use* (2015) [hereinafter ASAM, *National Practice Guideline*]; American Society of Addiction Medicine (ASAM), *National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use*, 9(5) J. Addiction Med. 358 (2015) [hereinafter ASAM, *National Practice Guideline*, J. Addiction Med.]; Substance Abuse and Mental Health Services Administration

- Psychological therapy by licensed professionals (individual, group, and family) and in collaboration with psychiatrists when necessary; and
- Social supports - case management and peer support to ensure complete evaluation and treatment of the patient and elimination of barriers to successful recovery.

309. Approximately 50% of patients with OUD who are initiating treatment first require detoxification services.

310. The current standard medical practice for treating opiate use disorders is a combination of addiction and recovery counseling and medications (MAT).[263]

311. The following paragraphs explain the standard treatment for OUD using MAT.

a. <u>The Medications for MAT</u>

312. The standard methodology for use of medications in treatment of addiction involving opioid use is more thoroughly set forth in the *ASAM National Practice Guideline For the Use of Medications in the Treatment of Addiction Involving Opioid Use*, 2015 American Society of Addiction medicine. Using medications for opioid withdrawal management is recommended over abrupt cessation of opioids.[264] Abrupt cessation of opioids often leads to strong cravings, which can lead to continued use.[265]

(SAMHSA), *Medication and Counseling Treatment*, https://www.samhsa.gov/medication-assisted-treatment/treatment.

[263] ASAM, *National Practice Guideline*, *supra* note 262; ASAM, *National Practice Guideline*, J. Addiction Med., *supra* note 262; SAMHSA, *Medication and Counseling Treatment*, *supra* note 262.

[264] ASAM, *National Practice Guideline*, *supra* note 262, at 6.

[265] *Id.*

313. There is strong support in the scientific literature for MAT.[266] Indeed, as the National Academies of Sciences, Engineering and Medicine Consensus Study Report concludes, "the literature is consistent in finding that the longer a person with OUD is treated and maintained on medication for a disorder, the better are their health consequences."[267]

314. There are three primary medications involved in the treatment of opiate use disorder:

i. methadone;

ii. buprenorphine;

iii. naltrexone.

315. Each of these medications has been demonstrated to substantially improve the efficacy of opiate use disorder treatment, typically doubling one-year sobriety rates.[268]

b. Methadone:

316. Methadone (Dolophine or Methadose) is a slow-acting opioid agonist.[269] Methadone is an effective treatment for opioid withdrawal management and the treatment of

[266] NASEM, *Pain Management and the Opioid Epidemic*, *supra* note 62, at 232 (*citing* 2009 Cochrane review; Weiss 2011; Fiellin et al. 2006; Nielson 2017 at 967; Schwartz et al. 2012; Wilson et. Al 2010).

[267] NASEM, *Pain Management and the Opioid Epidemic*, *supra* note 62, at 234.

[268] ASAM, *National Practice Guideline*, *supra* note 262, at 358–367.

[269] *Id.* at 29.

opioid use disorder.[270] Mean response at one year is approximately 60%, but may vary based on patient adherence factors or provider dosing practices.[271]

317. Methadone is taken orally so that it reaches the brain slowly, dampening the euphoria that occurs with other routes of administration while preventing withdrawal symptoms.[272] Additionally, tolerance does not increase for methadone the way it does for other opioids.[273]

318. Methadone has been used since the 1960s to treat heroin addiction and remains an effective treatment option.[274] Many studies have demonstrated its superiority to using abstinence-based approaches.[275]

319. Methadone is only available through federally approved OTPs, where it is dispensed to patients on a daily or almost daily basis in the initial stages of treatment. Federal and State laws allow take-home doses for patients who have demonstrated treatment progress and are judged to be at low risk for diversion.[276] Methadone is a treatment option recommended

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[270] *Id.*

[271] NASEM, *Pain Management and the Opioid Epidemic*, *supra* note 62, at 232.

[272] ASAM, *National Practice Guideline*, *supra* note 262, at 358–367.

[273] NASEM, *Pain Management and the Opioid Epidemic*, *supra* note 62, at 234.

[274] *Id.*

[275] ASAM, *National Practice Guideline*, *supra* note 262, at 358–367 (citing Mattick R, Breen C, Kimber J, et al. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database System Rev 2009. CD002209); NASEM, *Pain Management and the Opioid Epidemic*, *supra* note 62, at 234 (citing Hubbard and Marsden 1986; IOM 1995; Sells et al., 1979); Mattick et al. 2009; Bart 2012; Strang et al 2010).

[276]ASAM, *National Practice Guideline*, *supra* note 262, at 29.

for patients who are physiologically dependent on opioids, able to give informed consent, and who have no specific contraindications for agonist treatment when it is prescribed in the context of an appropriate plan that includes psychosocial intervention.[277] Methadone is recommended for patients who may benefit from daily dosing and supervision in an OTP, or for patients for whom buprenorphine for the treatment of opioid use disorder has been used unsuccessfully in an OTP or OBOT setting.[278]

320. Opioid withdrawal management in cases in which methadone is used to manage withdrawal symptoms must be done in an inpatient setting or in an OTP.[279] OTP regulations require monitored medication administration until the patient's clinical response, and behavior demonstrates that the prescribing of nonmonitored doses is appropriate.[280]

c. Buprenorphine:

321. Buprenorphine is also highly recommended for the treatment of opioid use disorder.[281] Buprenorphine relieves drug cravings without producing the euphoria or dangerous side effects of other opioids.[282] In addition to its pharmacological properties, an important feature of buprenorphine is its ability to be prescribed in office-based treatment settings.[283] This

[277] *Id.* at 7.

[278] *Id.*

[279] *Id.*

[280] *Id.* at 8.

[281] *Id.* at 32.

[282] *Id.*

[283] *Id.*

makes the medication more accessible to patients in certain locations where there are a lack or shortage of methadone clinics.

322. The US FDA approved buprenorphine in 2002, making it the first medication eligible to be prescribed by certified physicians through the Drug Addiction Treatment Act of 2000 (DATA 2000).[284] Through DATA 2000, physicians may apply for waivers to prescribe certain narcotic schedule III, IV, or V medications, including buprenorphine, from their office settings.[285] This provision of the act expands accessibility of community-based treatment options and mitigates the need to receive treatment through more specialized, and often less available, OTPs.[286] However, buprenorphine may also be administered in an OTP setting with structure and administration requirements identical to those for methadone.[287]

323. Buprenorphine has been associated with improved patient outcomes when compared with placebo.[288]

324. Patients who are administered buprenorphine should be seen frequently at the beginning of their treatment.[289] Many patients will require treatment for at least 2-5 years, and some patients for lifetime given the risk of relapse and mortality associated with not being on MAT.

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[284] *Id.*

[285] *Id.*

[286] *Id.*

[287] *Id.*

[288] NASEM, *Pain Management and the Opioid Epidemic, supra* note 62, at 235 (citing Thomas et al. 2014).

[289] ASAM, *National Practice Guideline, supra* note 262, at 7.

d. Naltrexone:

325. Naltrexone is a long-acting opioid antagonist that may be used to prevent relapse to opioid use.[290] Naltrexone blocks the effects of opioids if they are used.[291] Naltrexone is available in oral (ReVia, Depade) and extended-release injectable (Vivitrol) formulations[292].

326. A few studies that found oral naltrexone effective were conducted in situations in which patients were highly motivated, were legally mandated to receive treatment, and/or taking the medication under the supervision of their family or significant others.[293] A meta-analysis of 1158 participants in 13 randomized trials compared treatment with oral naltrexone to either placebo or no medication for opioid use disorder.[294] The evidence generated from these trials was limited by poor adherence and high dropout rates.[295] Oral naltrexone was more efficacious than placebo in sustaining abstinence in three trials in which patients had external mandates (e.g., legal requirements) and were monitored in adhering to daily doses of the medication.[296]

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[290] *Id.* at 35.

[291] *Id.*

[292] *Id.*

[293] *Id.*

[294] *Id.* (citing S. Minozzi et al., *Oral Naltrexone Maintenance Treatment For Opioid Dependence*, Cochrane Database Sys. Rev. at CD001333 (2011)).

[295] *Id.*

[296] *Id.* (citing S. Minozzi et al., *Oral Naltrexone Maintenance Treatment For Opioid Dependence*, Cochrane Database Sys. Rev. at CD001333 (2011); Y. Adi, et al., *Oral Naltrexone As A Treatment For Relapse Prevention In Formerly Opioid-Dependent Drug Users: A Systematic Review And Economic Evaluation*, Health Technology Assess 2007; 11. iii–iv, 1–85).

Agent	Dose	Dosing
Buprenorphine sublingual film, tablets (generic)	PO: 2 mg, 8 mg film and tablets	**Initial:** 2–4 mg (Increase by 2–4 mg) **Daily:** ≥8 mg **Max:** 24 mg/day
Methadone tablets/liquid (generic)	PO: 5 mg, 10 mg, tablets; 10 mg/mL liquid	**Initial:** 10-30 mg (Reassess in 3–4 hours; add ≤10 mg PRN) **Daily:** 60-120 mg[a]
Naltrexone XR injection *(Vivitrol®)*	IV/IM: 380 mg in 4 cc	Every 4 weeks
Naltrexone tablets (generic)	PO: 50 mg	**Daily:** 50 mg (May give 2–3 daily doses at once on M–W–F.)

327. Patients treated with methadone are treated in a clinic 7 days per week. A normal course for methadone treatment is to administer this treatment for at least two and as many as twenty or more years. Patients who are identified as stable may receive some "take home doses" of methadone and therefore not need to continue on daily attendance. Access to these "take home doses" is carefully controlled by federal and state regulations.

328. Patients treated with Buprenorphine are typically administered the medication on an outpatient basis. Medication is taken by the patient daily and overseen by the prescribing clinician. Patients are recommended to stay on buprenorphine for a minimum of 2 years and a maximum that is undefined. Patients are monitored and overseen by clinicians on a weekly to monthly basis. After more than a year of stability, patients may be permitted to receive a refill or even two and thus be seen every other or every third month. Urine toxicology and prescription monitoring program (PMP) checks are required.

329. Naltrexone is administered by monthly prescription or monthly injection. Periodic toxicology, PMP, and liver function checks also take place. Typically, naltrexone is recommended for at least one year and often for two.

e. Biopsychosocial Treatment

330. In addition to medication administration, patients need varying levels of treatment to accompany the medications. There are well-established guidelines that determine the levels of care and elements of treatment for the management of patients with OUD moderate to severe that have been promulgated and disseminated by the Ohio Department of Mental Health and Addiction Services and the American Society of Addiction Medicine ("ASAM") through their patient placement criteria.[297]

331. ASAM's treatment criteria provide separate placement criteria for adolescents and adults to create comprehensive and individualized treatment plans[298]. Adolescent and adult treatment plans are developed through a multidimensional patient assessment over five broad levels of treatment that are based on the degree of direct medical management provided, the structure, safety and security provided and the intensity of treatment services provided.[299] Those treatment levels are set forth by ASAM as follows:[300]

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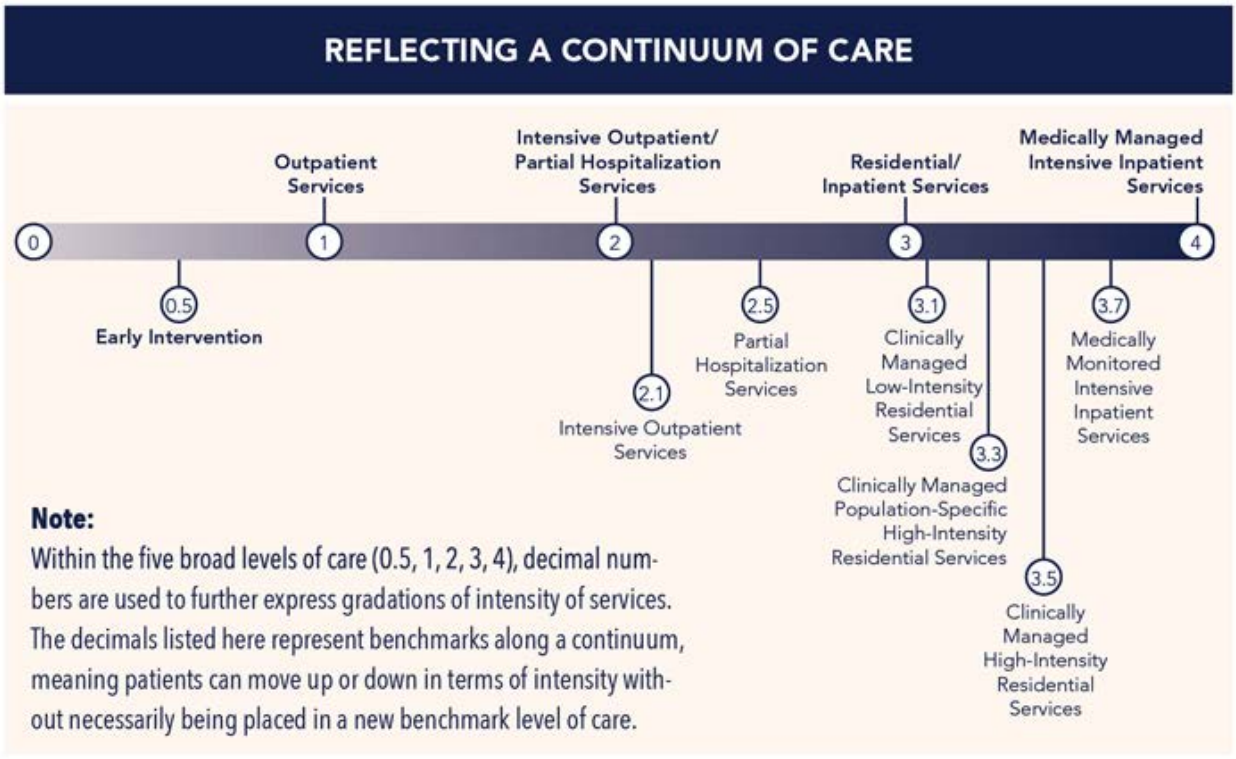
[297] *ASAM Patient Placement Criteria: Supplement on Pharmacotherapies for Alcohol Use Disorders* (Marc J. Fishman et al. eds., 2010), https://books.google.com/books?isbn=1451161263; U.S. Dept. Health & Human Serv., *Pain Management Inter-Agency Task Force: Meeting Materials – Environmental Scan Report*, https://www.hhs.gov/ash/advisory-committees/pain/meetings/2018-05-30/environmental-scan-report/index.html.

[298] *What is the ASAM Criteria?*, American Society of Addiction Medicine, https://www.asam.org/resources/the-asam-criteria/about.

[299] *Id*.

[300] *Id*.



332. The treatment setting described as level 1 treatment may be a general outpatient ("OTP") location such as a clinician's practice site.[301] The setting described as level 2 in the ASAM Criteria may be an intensive outpatient treatment ("IOP") or partial hospitalization program ("PHP") housed in a specialty addiction treatment facility, a community mental health center, or another setting.[302] The ASAM Criteria describes level 3 or level 4 treatment, respectively, as a residential addiction treatment facility or hospital.[303]

[301] ASAM, *National Practice Guideline*, *supra* note 262, at 5-6.

[302] *Id.*

[303] *Id.*

333. Opioid treatment programs (OTPs) offer daily supervised dosing of methadone, and increasingly of buprenorphine.[304] In accordance with the Federal law (21 CFR §1306.07), office-based opioid treatment (OBOT), which provides medication on a prescribed weekly or monthly basis, is limited to buprenorphine.[305] Naltrexone can be prescribed in any setting by any clinician with the authority to prescribe any medication.[306] A patient's psychosocial situation, co-occurring disorders, and risk of diversion determine whether OTP or OBOT is most appropriate.[307]

334. Patients in the OUD populations typically break down along the following lines with respect to the level of care necessary for treatment:

i. Approximately 30% of patients with Opioid Use Disorder need IOP levels of care along with MAT (Level 2 Treatment) [308]

ii. Another 30% typically require PHP level of care, or brief 1 to 2 week residential treatment followed by PHP, and then IOP levels of care along with MAT (Level 2.5).[309]

iii. Another 30% of patients often require fairly extensive residential treatment with MAT, for 4 weeks to six month's duration, followed by PHP stabilization and

[304] ASAM, *National Practice Guideline*, *supra* note 262.

[305] *Id.*

[306] *Id.*

[307] *Id.*

[308] *Id.*

[309] *Id.*

IOP outpatient treatment with MAT.[310] Factors influencing whether patients need longer-term residential treatment include the presence of a psychiatric dual diagnosis, more extensive morbidity from the opioid use disorder, a lack of stable sober support in the community, and the degree to which the opiate use disorder has progressed in severity.

335. In my clinical experience, recovery housing is an important step in the treatment process for some individuals with OUD. Any plan to address the opioid epidemic should include recovery housing for at least 30% of the population being treated, with a minimum stay of two months per individual.

336. The above outlined opiate use disorder MAT treatment approach can be provided in conjunction with incarceration as part of the experience while incarcerated and part of the probationary or parole experience once released. This is termed "pre-release treatment" followed by drug court post-release treatment. The efficacy of pre-release treatment followed by drug court post-release is well-established.[311] It requires close monitoring, as described above, with toxicology testing and an expectation of full adherence with the plan, but it can markedly

[310] *Id.*

[311] T.C. Green et al., *Postincarceration Fatal Overdoses After Implementing Medications for Addiction Treatment in a Statewide Correctional System*, 75 JAMA Psychiatry 4, 405–407 (2018), doi:10.1001/jamapsychiatry.2017.4614.

improve recovery rates and decrease subsequent overdose events.[312] This is essential, since the leading cause of death after incarceration is accidental overdose on opioids.[313]

f. Necessary Monitoring

337. Opiate Use Disorder treatment with MAT involves extensive monitoring, including frequent toxicology testing intensively in the early months and less frequently thereafter. Any positive toxicology tests should result in the patient being re-assessed and likely referred back to the next higher or more intensive level of treatment.

g. Relapse Rates

338. Treating those suffering addictive disease involving opioids must take into account the high level of relapse experienced in the addicted population. Indeed, after treatment, year one rates are in the range of 40%-80%, even in patients who participate in IOP. The lower ranges are seen in those in IOP and on MAT who do not have psychiatric dual diagnosis. The higher rates occur in those without the afore-mentioned predictors of a positive outcome. With each subsequent treatment experience, however, additional percentages of patients become sober, so that the accumulative rate of sobriety can eventually reach 60-70% (of those who have survived of course) of the patients who relapse..[314]

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[312] *Handbook of Evidence-Based Substance Abuse Treatment in Criminal Settings* (Carl Leukefeld, Thomas P. Gullotta & John Gregrich eds., 2011), https://books.google.com/books?isbn=144199470X; H. Matusow et al., *Medication assisted treatment in US drug courts: Results from a nationwide survey of availability, barriers and attitudes*, 44(5) J. Substance Abuse Treatment 473 (2013).

[313] I.A. Binswanger et al., *Mortality After Prison Release: Opioid Overdose and Other Causes of Death, Risk Factors, and Time Trends From 1999 to 2009*, 159 Annals Internal Med. 592 (2013).

[314] Yih-Ing Hser et al., *A 33-Year Follow-up of Narcotics Addicts*, 58 Archives Gen. Psychiatry 503 (2001).

h. Referral to Treatment

339. As discussed above, access to treatment is a significant barrier affecting outcomes in the addicted population. It is important to ensure that patients needing treatment get access to that treatment as soon as possible, if not immediately. This is particularly true with patients who have experienced an overdose or other detrimental health effect related to the opioid narcotic.

340. Patients who have had an acute accidental overdose on opioids may be resistant to comprehensive addiction treatment in the short-term, but they often are more agreeable to medications, especially methadone maintenance or buprenorphine maintenance in a harm-reduction venue rather than in a treatment or MAT venue.

341. Patients who have had overdoses are best approached in the emergency room at the time of the overdose and offered the ability to immediately begin harm reduction focused medication treatment. This requires close collaboration between emergency room clinicians, outpatient buprenorphine or methadone outpatient clinics often times bridged by daily house calls to continue with administration of buprenorphine and motivational interviewing. Recovery coaches, or individuals who are trained to do motivational interviewing and who are in recovery themselves, are also extremely useful in emergency room settings and in outreach to individuals who have had an opioid overdose.

342. This process is sometimes referred to as component of Screening, Brief Intervention, and Referral to Treatment ("SBIRT").[315] SBIRT is an approach to the delivery of early intervention and treatment to people with substance use disorders and those at risk of developing these disorders. SAMSHA defines the three components as:

[315] Substance Abuse and Mental Health Services Administration, *Screening, Brief Intervention, and Referral to Treatment (SBIRT)*, https://www.samhsa.gov/sbirt.

i. Screening quickly assesses the severity of substance use and identifies the appropriate level of treatment.

ii. Brief intervention focuses on increasing insight and awareness regarding substance use and motivation toward behavioral change.

iii. Referral to treatment provides those identified as needing more extensive treatment with access to specialty care.

343. It is very important for patients who have been identified as having OUD, especially patients who have experienced an overdose situation, to receive immediate screening and referral to treatment. Thus, it is important that communities have recovery coaches or other qualified individuals actually present in the Emergency Room or other acute care medical setting, who can help motivate and immediate assist patients with access to the appropriate treatment. This produces "just in time" availability of SBIRT interventions in order to decrease the patient's internal hesitance and the system's external barriers to "treatment on demand".

i. Treating the Dependent Population

344. It is critical to any treatment solution to not only take into account the individuals that meet the strict definition of moderate to severe OUD or addiction, but also those who classify as mild OUD or are physically dependent on opioids. Indeed, providing a solution only for those who meet the strict definition of addiction today would expose communities to long-term continuation of the epidemic in failing to treat and prevent harm for the dependent or misusing populations, because not only is opioid physical dependence and opioid misuse a serious and costly problem currently, but those populations are at risk of developing OUD in the future.

345. As fully outlined above, removing patients who have been taking opioids for long periods of time or at high doses is extremely difficult. That population of patients must be

addressed, however, with treatment solutions designed to conduct the long-term taper and removal from opioids, in conjunction with MAT treatment or other addiction treatment modalities where necessary.

2. Harm Reduction

a. Naloxone.

346. Another critically important aspect of addressing the current opioid epidemic is the provision of naloxone anti-overdose rescue kits to patients with opiate use disorder, family members of patients with opiate use disorder, individuals in treatment for opiate use disorder, individuals being released from incarceration who have a history of opiate use disorder, and all first responders in a community. These naloxone kits have been demonstrated to reverse opioid overdoses in the field and improve patient outcomes, including decreasing fatality rates. The naloxone anti-overdose kits need to be widely disseminated throughout the addictive community, as well as the community in general. There is less evidence to support the provision of naloxone to routine patients who have been prescribed opioid analgesics.

347. The provision of naloxone anti-overdose kits has decreased death rates, decreased episodes of anoxic brain damage from opioid overdoses, and improved patients' quality of life.

348. There is no evidence that the provision of naloxone has any deleterious public health effects whatsoever.

349. The provision of naloxone widely in the opiate use disorder community and amongst first responders is an evidence-based ethical compassionate approach to try to save the lives of individuals enmeshed in active opiate use disorders.

350. Any naloxone distribution system should focus on getting naloxone to at risk patients and their family members/closest friends. Factors that have been useful in identifying at

risk patients in the following groups who then should be prescribed or dispensed a naloxone rescue kit are as follows:

i. Previous opioid intoxication or overdose

ii. History of nonmedical opioid use

iii. Initiation or cessation of methadone or buprenorphine for opioid use disorder treatment.

iv. Higher-dose (>50 mg morphine equivalent/day) opioid prescription.

v. Receiving any opioid prescription plus:

vi. Rotated from one opioid to another because of possible incomplete cross-tolerance.

vii. Smoking, COPD, emphysema, asthma, sleep apnea, respiratory infection or other respiratory illness.

viii. Renal dysfunction, hepatic disease, cardiac illness or HIV/AIDS.

ix. Known or suspected concurrent alcohol use.

x. Concurrent benzodiazepine or other sedative prescription.

xi. Concurrent antidepressant prescription.

xii. Patients who may have difficulty accessing emergency medical services (distance, remoteness).

xiii. Voluntary request from a family member, friend, peace officer or other person in a position to assist an individual who there is reason to believe is at risk of experiencing an opioid-related overdose

351. At a minimum, the at-risk population should include all persons in the community with Opioid Use Disorder (addiction), misuse or dependence - all of whom fulfill at least some of the criteria above.

352. Doses Per At Risk Individual: Best estimates demonstrate that for every person identified with Dependence as well as Misuse/Use disorder, administrators should plan for between 3 and 9 doses of naloxone per person. These doses per person are best allocated between patient and loved ones, close friends, or relatives.

353. Supply to High Impact Centers: A key to harm reduction by distribution of naloxone is getting these lifesaving medications to the correct sources. There are key distribution points that must be included in a Naloxone allocation system for maximum harm reduction. Those include:

i. Syringe exchange programs

ii. Jail

iii. Emergency department

iv. First responders including the fire department, EMS, and law enforcement.

354. Personnel to Distribute: The workforce capacity to distribute the medication must also be considered and is generally not currently in place. Public health departments are the most capable of coordinating such efforts, however, additional employees will likely be necessary to run the county or city's Naloxone distribution program.

3. Prevention-Provider Education

355. Prevention is the third aspect of a comprehensive approach to solving the current opiate use disorder epidemic.

356. Prevention includes educating the public regarding non-opioid treatments for various pain syndromes. It also involves educating clinicians: about non-opioid approaches to addressing various pain syndromes; about strategies to minimize or decrease the use of opioids when they are necessary; to screen more appropriately for opiate use disorder and to not provide controlled drugs to patients with addictive disease or who are already misusing opioids or other drugs; on how to refer patients with substance-use disorders for appropriate counseling and treatment; on how to taper people off of opioids and benzodiazepines; on how to manage opioid and benzodiazepine withdrawal so that patients can be treated in a reasonably comfortable compassionate way; on medication-assisted treatment ("MAT"); and on how to play a role providing MAT to patients with opiate use disorders as they attempt to achieve and maintain sobriety.

RESERVATION OF RIGHTS

This report is a statement of opinions I expect to express in this matter and the basis and reasons for those opinions. This report summarizes only my current opinions and analyses to date, which are subject to change depending upon ongoing discovery and additional information. I respectfully reserve the right to supplement my report in light of this and any other additional fact discovery, opinions by other experts, and/or trial testimony. I also respectfully reserve the right to provide rebuttal opinions and testimony in response to other experts, and rebuttal testimony in response to any fact witnesses. In connection with my anticipated trial testimony in this action, I may use as exhibits various documents produced in this litigation that refer to or relate to the matters discussed in this report. In addition, I respectfully reserve the right to use animations, demonstratives, enlargements of actual attachments, and other information in order to convey my opinions.

I understand that I may be asked to provide further opinions and analyses on other issues, including in response to analyses provided by other experts. I will do so at the appropriate time set by the court.

Executed on this 25th day of March, 2019, in Cleveland, Ohio.

Theodore Parran, M.D.